The Synthesis of Substituted Phosphonic Acids

by

Jane Hanrahan

Submitted for the Degree of Doctor of Philosophy

Department of Chemistry
University of Warwick
August 1995

Dedicated to the memory of Dr David Hutchinson

Contents

List of Figures

List of Tables;

Acknowledgements

I would like to express my deepest gratitude to the late Dr D. W. Hutchinson who encouraged me to start this work and whose memory encouraged me to complete it. I would also like to thank Dr P. C. Taylor and Professor D. H. G. Crout for taking on the supervision of this project and for their advice and encouragement during the course of my studies.

Thanks is also due to Mr P. Moore for doing the microanalyses, Dr J. Hastings for running some of the nmr spectra, Mr I. Katyal for the mass spectra, Dr W. E. Errington for doing the X-ray crystallography and Dr A. Easton in the Department of Biological Sciences Warwick University, for carrying out the antiviral assays.

I would also like to thank all my colleagues in the department of chemistry, both past and present, for providing amusement and encouragement and generally making it a fun place to work. Last but not least, a special thankyou to Derek Pert for his help and encouragement during the course of this work and for finding other things to do while I completed this thesis.

Declaration

The work described in this thesis is the original of the author, except where acknowledgement has been made to results and ideas previously published. The work was carried out at the Department of Chemistry, University of Warwick, between January 1st, 1991 and December 30th, 1994 and has not been previously submitted for a degree at any institution.

Abstract

Cyclic phosphonic acid analogues of the endogenous amino acids *L*-aspartic acid and *L*-glutamic acid have played a major role in the characterisation of excitatory amino acid receptors in the central nervous system. The aim of the first section of this work is to describe the development of a synthetic route that gives access to a novel series of compounds, 3-substituted-cyclobutanephosphonic acids. The synthesis of a valuable intermediate diethyl 3-oxocyclobutanephosphonate is described. Elaboration of the ketone functionality of this compound provides allows the synthesis of a number of previously inaccessible 3-substituted-cyclobutanephosphonates, including *E*- and *Z*-3-amino-3-carboxy-cyclobutanephosphonic acid, 3-amino-cyclobutanephosphonic acid and the four stereoisomers of 3-(amino-carboxy-methyl)-cyclobutanephosphonic acid. Enzymatic hydrolysis of the phenylacetyl derivative of diethyl 3-(amino-cyanomethyl)-cyclobutanephosphonate by penicillinacylase allowed the preparation of 3-(amino-carboxy-methyl)-cyclobutane-phosphonic acid with high enantiomeric purity.

The antiviral activity of phosphonoacetic acid (PAA) has long been recognised. However, a number of problems are associated with the administration of this compound as an antiviral, these include high toxicity to the hosts cells, poor uptake in to cells and absorbtion by teeth and bones. One approach to solving some of these problems may be to make the compounds more lipophilic by increasing the number of carbon atoms in the molecule. The synthesis of a number of cyclic analogues of PAA and the related bisphosphonic acids is described. These compounds are prepared by phase transfer catalysed alkylation of trialkyl phosphonoacetate and tetra alkyl methylenebisphosphonate. The antiviral activity of these compounds against Herpes simplex virus 1 (HSV1) was investigated.

A series of chiral at sulfur, α-phosphoryl sulfoxides and β-hydroxy sulfoxides were prepared. These compounds were investigated for their ability to enantioselectively catalyse the reaction between diethylzinc and benzaldehyde. Although this reaction was catalysed by all of these compounds, this action was not accompanied by enantioselectivity. Comparison of our results with those obtained for β-hydroxy sulfoximides enabled this lack of enantioselectivity to be explained by the analysis of the proposed transition state complexes.

Abbreviations

(HO)-AEP	2-Amino-1-hydroxyethylphosphonic acid
5-HPCA	(*RS*)-3-Hydroxy-4,5,6,7-tetrahydroisoxazolo [5,4-*c*] pyridine-5-carboxylic acid
7-HPCA	(*RS*)-3-Hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*] pyridine-7-carboxylic acid
2,3-PDA	2,3-piperidinedicarboxylic acid
α–AA	α-Aminoadipate
ACE	Angiotensin converting enzyme
ACPD	1-Aminocyclopentane-1,3-dicarboxylic acid
ACPP	1-Aminocyclopropanephosphonate
ACPP	3-Amino-3-carboxycyclopentylphosphonic acid
AEP	Aminoethanephosphonic acid
AIDS	Acquired immune deficiency syndrome
Ala-P	1-Aminoethylphosphonic acid
AMNH	((*RS*)-2-amino-3-[2-[3-methyl-3-oxoisoxazolin-4-yl)-methyl]-5-methyl-3-oxoisoxazolin-4-yl]propionic acid
AMOA	(*RS*)-2-Amino-3-[3-carboxymethyl-5-methylisoxazol-4-yl]propionic acid
AMPA	*L*-α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP3	2-Amino-3-phosphonopropanoic acid
AP4	2-Amino-4-phosphonobutanoic acid
AP5	2-Amino-5-phosphonopentanoic acid
AP6	2-Amino-6-phosphonohexanoic acid
AP7	2-Amino-7-phosphonoheptanoic acid
aq	Aqueous
AZT	3'-Azido-2',3'dideoxythymidine
BMAA	β-*N*-methyl-amino-L-alanine
BOAA	β-*N*-oxalylamino-L-alanine
BuLi	Butyllithium
c	Concentration (g/100ml)
CAN	Ceric ammonium nitrate
cat.	Catalyst
CCG	α-(Carboxycyclopropyl)glycine
CGP 37849	2-Amino-4-methyl-5-phosphono-3-pentenoic acid
CGS 19755	*cis*-4-Phosphonomethyl-2-piperidine carboxylic acid
CNQX	6-Cyano-7-nitroquinoxaline-2,3-dione
CNS	Central nervous system

CPP	3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid
CPPene	3-(2-Carboxypiperazin-4-yl)propenyl-1-phosphonic acid
DAIB	(Dimethylamino)isoborneol
DET	Diethyl tartrate
ddC	2',3'-Dideoxycytidine
ddI	2',3'-Dideoxyinosine
DMF	*N,N*-Dimethylformamide
DNA	Deoxyribonucleic acid
DNJ	Deoxynojirimycin
DNQX	6,7-Dinitroquinoxaline-2,3-dione
DOPA	3,4-Dihydroxyphenylalanine
EAA	Excitatory amino acid
γ-DGG	γ-*D*-glutamylglycine
GABA	γ-Aminobutyric acid
GTP	Guanosine triphosphate
HMPA	Hexamethylphosphoramide
HSV	Herpes simplex virus
IP_3	Inositol 1,4,5-triphosphate
L-asp-β-HA	*L*-Aspartate-β-hydroxamic acid
LDA	Lithium di-*iso*propylamide
MeCN	Acetonitrile
MeOH	Methanol
mol	Mole
mRNA	Messenger ribonucleic acid
NAAG	*N*-acetylaspartylglutamic acid
NMDA	*N*-Methyl-*D*-aspartic acid
nmr	Nuclear magnetic resonance
PAA	Phosphonacetic acid
PFA	Phosphonoformic acid
PFU	Plaque forming unit
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
RNA	Ribonucleic acid
RT	Room temperature
SOP	*L*-Serine-*O*-phosphate
TEBACl	Benzyltriethylammonium chloride
TFA	Trifluoracetic acid
TFMC	[3-(trifluoromethylhydroxymethylene-*d*-camphorato]-europium(III)

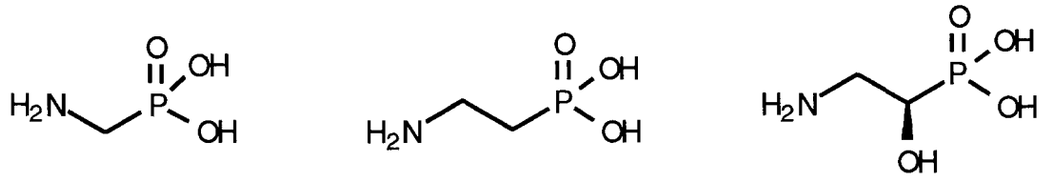
THF	Tetrahydrofuran
TMEDA	Tetramethylethyl diamine
TMS	Tetramethylsilane
TMSBr	Trimethylsilyl bromide
TMSI	Trimethylsilyl iodide
VZV	Varicellar zoster virus
$[\alpha]_D$	Specific rotation at 589 nm

Chapter 1

Introduction

1.1. Biologically Active Phosphonic Acid Analogues of Amino Acids

Aminoalkanephosphonic acids (Figure 1.1) are broadly defined as analogues of amino acids in which a carboxylic group is replaced by a phosphonic (or related) group. Although they were first mentioned in the literature in 1943 in a patent describing the synthesis of aminomethanephosphonic acid **(1)**,[1] interest in these compounds increased during the 1960s with the discovery of 2-aminoethanephosphonic acid (AEP) **(2)** in cultures of *Tetrahymena thermophila*. Since that time AEP has been found in a variety of living organisms from micro-organisms to marine creatures and mammals, including humans[2] and its biosynthesis has been studied in detail.[3] More recently, the related compound, 2-amino-1-hydroxyethylphosphonic acid ((HO)-AEP) **(3)** has been isolated from cultures of *Acanthamoeba castellanii*.[4, 5] However, it was during the 1970s that the wide range of biological activities of both synthetic and natural aminophosphonic acids became apparent.



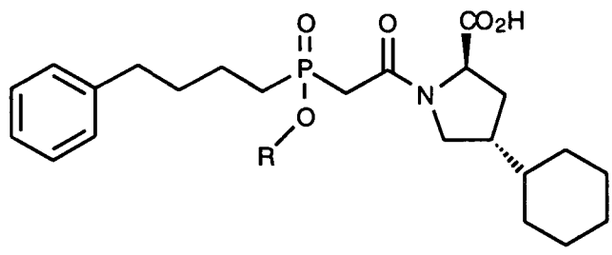
(1) **(2)** **(3)**

Figure 1.1: Aminomethanephosphonic acid (1) , AEP (2) and (HO)-AEP (3)

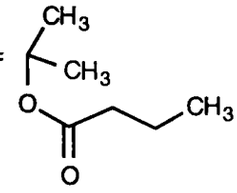
Because they are structural analogues of amino acids, aminophosphonic acids usually act as their antagonists and compete with their carboxylic counterparts for the active sites of enzymes or other cell receptors. As inhibitors of metabolic processes, they exert their physiological activity as antibacterial agents, neuroactive compounds, anticancer drugs or pesticides.

1.1.1. Enzyme Inhibition and Antimicrobial Activity of Aminophosphonic Acids

The concept that phosphonic and phosphinic acids mimic the putative tetrahedral transition states of enzyme reactions taking place at carbonyl groups of carboxylic acids has proven an effective basis for designing potent enzyme inhibitors. The compound (Figure 1.2) that represents the most successful commercial implementation of the concept of a transition state analogue is Fosinopril **(4)**, an inhibitor of angiotensin converting enzyme (ACE).[6] This compound is a derivative of 2-phosphonopyrrolidine, the phosphonic acid analogue of proline. Fosinopril **(4)** is an acyloxy prodrug of the active compound, which is metabolised to the active phosphonic acid **(4a)** by intestinal and hepatic esterases. It has been proposed that the phosphinyl function coordinates to the zinc ion at the active site of the enzyme and approximates the tetrahedral geometry of the hydrated amide transition state resulting from the addition of water to the scissile amide bond of the substrate, resulting in inhibition of the enzyme.[7]



(4) Fosinopril R=

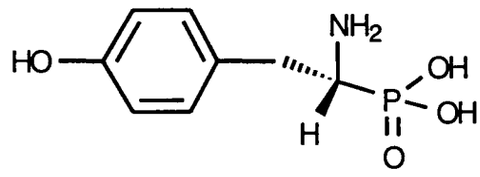


(4a) Active ACE inhibitor R=H

Figure 1.2: Angiotensin Converting Enzyme Inhibitor

1-Aminocyclopropanephosphonate (ACPP) has been prepared synthetically. It is the phosphonic acid analogue of 1-amino cyclopropanecarboxylate, a compound that is found in trace amounts in the tissues of many plants. The effect of ACPP on pyridoxal 5'-phosphate linked enzymes has been investigated. ACPP was found to be a potent inhibitor of 1-aminocyclopropanecarboxylate deaminase from *Psuedomonas* sp. and alanine racemase from *Bacillus steaothermophilus*.[8] More recently the synthesis of a large number of 2-substituted- and 2,3-disubstituted-1-aminocyclopropylphosphonic acids has been described. However, no biological data has yet been reported.[9]

The only known naturally occurring α-aminophosphonic acid (Figure-1.3) is (*R*)-(-)-1-amino-1-(4-hydroxyphenyl)ethylphosphonic acid **(5)**, the phosphonic acid analogue of tyrosine. This compound was identified as a novel amino acid in two tripeptides with antihypertensive activity isolated from cultures of Actinomycetes K-26 and *Actinommadura spiculaspora*.[10]

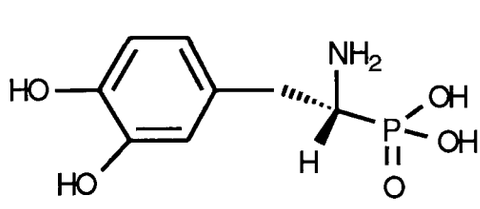


(5)

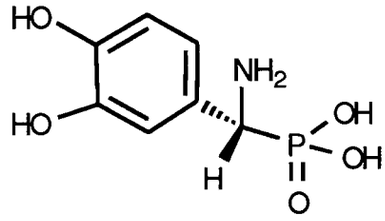
Figure 1.3: (*R*)-(-)-1-Amino-1-(4-hydroxyphenyl)ethylphosphonic Acid (5)

Although many phosphonic acid analogues of naturally occurring amino acids act as inhibitors of enzymes, it has also been reported that structural differences between phosphonic and carboxylic groups do not prevent aminophosphonic acids serving as substrates for enzymes that normally utilise amino acids. The relatively few reported examples include only reactions that proceed without direct participation of the carboxylic (or phosphonic) function. 1-Amino-(2-(3,4)-dihydroxyphenyl)ethylphosphonic

acid (Figure 1.4) **(6)**, the phosphonic acid analogue of *L*-3,4-dihydroxyphenylalanine (*L*-DOPA), has been found to be converted into a melanin like-compound by the enzyme tyrosinase from mushrooms. Shortening of the alkyl chain by one methylene unit gave amino-((3,4)-dihydroxyphenyl)methylphosphonic acid **(7)**, one of the most powerful inhibitors of this enzyme.[11]



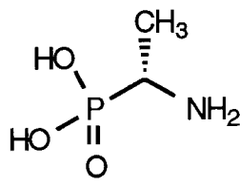
(6)



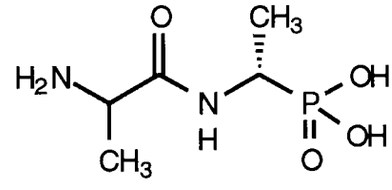
(7)

Figure 1.4: 1-Amino-(2-(3,4)-dihydroxyphenyl)ethylphosphonic Acid (6) and Amino-((3,4)-dihydroxyphenyl)methylphosphonic Acid (7)

The inhibition of enzymes is also the underlying mechanism for a variety of aminophosphonic acids (Figure 1.5) that act as antibiotics. The group of enzymes known as alanine racemases are an attractive target for antibacterial drug development. These enzymes operate in the early stages of cell growth. By catalysing the racemisation of alanine they provide *D*-alanine for inclusion in to the bacterial cell wall. The phosphonic acid analogue of alanine, *L*-1-aminoethylphosphonic acid (Ala-P) **(8)**, along with alafosfolin **(9)**, a synthetic peptide incorporating Ala-P, have been found to be potent inhibitors of a racemase from Gram-positive bacteria.[12]



(8)



(9)

Figure 1.5: Inhibitors of Alanine Racemase

A number of natural antibiotic aminophosphonic acids produced by a variety of micro-organisms have been identified (Figure 1.6). Many of these natural aminophosphonic acids are incorporated in to small peptides. These include; bialaphos **(10)** (*Streptomyces viridochromogenes*),[13] phosalacine **(11)** (*Kitasporia phosalacinea*),[14] phosphinothricin **(12)** (*S. hygroscopicus*),[15] plumbeomycins **(13)** (*S. plumbeus*),[16] the related rhizotocins **(14)** (*Bacillus subtilis*),[17] fosmidomycin **(15)** and other related compounds **(16-18)** (*S. lavendulae* and *S. rubellomurins*).[18]

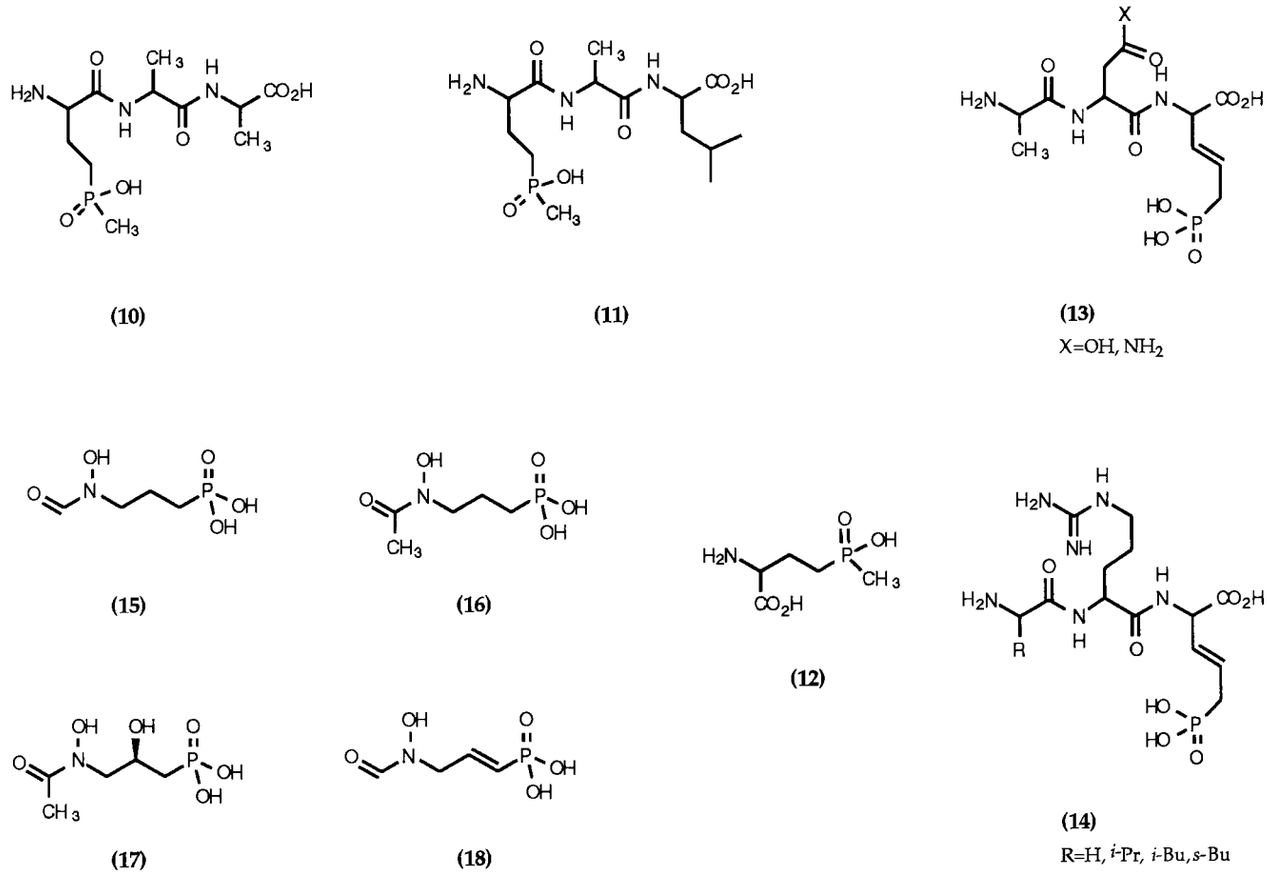


Figure 1.6: Naturally Occurring Aminophosphonic acids and Phosphonopeptides with Antibacterial Properties

The plumbeomycins **(13)** and rhizocticines **(14)** are groups of di- and tripetide antibiotics that are thought to interfere with threonine or threonine-related metabolism. The unusual aminophosphonic acid, *E*-2-amino-5-phosphono-3-pentenoic acid, a constituent of both rhizocticines and plumbeomycins, has been shown to irreversibly inhibit threonine synthase

from *Escherichia coli*. These data indicate that the toxicity of rhizocticines and plumbeomycins is due to inhibition of threonine synthase by *E*-2-amino-5-phosphono-3-pentenoic acid, which is liberated by peptidases after uptake into the cell.[19]

Fosmidomycin, 3-(*N*-formyl-*N*-hydroxyamino)propylphosphonic acid **(15)**, is a promising antibiotic. It is thought to inhibit the biosynthesis of an isoprenoid precursor (possibly farnesyl phosphate). This compound has already passed phase I tolerance trials and has been recommended for further clinical evaluation.[12] A number of related compounds have also been isolated from *Streptomycete* species. Of these 3-(*N*-acetyl-*N*-hydroxyamino)propylphosphonic acid **(16)** and (2*R*)-3-(*N*-acetyl-*N*-hydroxyamino)-2-hydroxypropylphosphonic acid **(17)** have weaker antibacterial action than fosmidomycin. 3-(*N*-Formyl-*N*-hydroxyamino)-1-*trans*-propenylphosphonic acid **(18)** has greater antibacterial activity than the previous two compounds, but is still less active than fosmidomycin **(15)**.[2]

Several phosphonopeptides are known to have potent antibacterial activity. Alafosfalin **(9)**, a synthetic phosphonopeptide containing the phosphonic acid analogue of alanine **(8)**, is probably the most intensively studied member of the phosphorus containing antibiotics. Extensive studies have established its usefulness in the treatment of urinary tract infections.[20] The mechanism of action of these phosphonopeptides involves active transport through the bacterial cell wall by means of peptide permeases and enzymatic cleavage of the peptide bond within the cell to liberate the active aminophosphonic acid. In the case of alafosfalin **(9)**, this is *L*-1-aminoethylphosphonic acid **(8)** which then inhibits alanine racemase. The naturally occurring peptide Bialaphos **(10)** releases phosphinothricin **(12)**, a phosphinic amino acid which is also produced by various *Streptomycete* species. It is a potent inhibitor of the enzyme glutamine synthase which converts glutamic acid to glutamine,[21] a reaction of primary importance in the

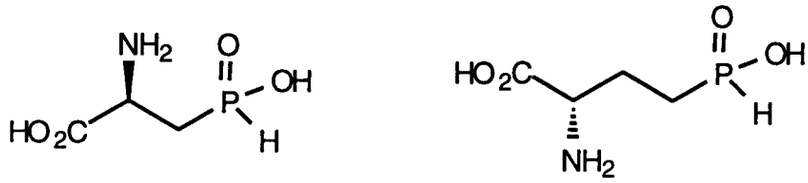
metabolism of nitrogen. Interaction of phosphinothricin with glutamine synthase occurs only under conditions in which phosphorylation can occur. This strongly suggests that further enzymatic modification occurs to produce phosphorylated phosphinothricin, which is thought to mimic a putative tetrahedral transition state of the enzymatic reaction.[12]

Since the wide range of biological activities of phosphinothricin **(12)** and related compounds were first reported, many further studies of both their biological activities and total synthesis have been carried out.[21] It has been discovered that the *L*-phosphinothricin is twice as active as the racemic mixture, indicating that the active enantiomer is the *L*-isomer. Many asymmetric syntheses of both antipodes of phosphinothricin have been reported using a variety of different methods to ensure optical purity.[21] These range from starting with the chiral pool compounds *L*-methionine, *L*-glutamic acid[22] or *L*-aspartic acid[23] or other chiral building blocks such as a chiral bis-lactim ether,[24] to asymmetric hydrogenation of phosphino α-acylmido acrylates[25] and enzymatic hydrolysis of amide, carboxylic and phosphinic ester intermediates.[15, 26, 27]

A number of α- and γ-substituted phosphinothricins have been prepared and their activity as inhibitors of glutamine synthetase investigated. Substitution in the α-position did little to change the inhibitory action of these compounds. However, activity was significantly reduced by substitution in the γ-position. Interestingly, *trans*-3-amino-3-carboxycyclohexylphosphinic acid, in which the α- and γ-positions are joined in a six-membered ring, showed similar activity to phosphinothricin.[28]

The phosphonous acid analogues (Figure 1.7) of both aspartic acid and glutamic acid, 1-amino-1-carboxyethanephosphonous acid **(19)** and 1-amino-1-carboxypropanephosphonous acid **(20)** respectively, have been isolated from *S. hygroscpicus*. The glutamic acid analogue has been shown to be an intermediate in the synthesis of phosphinothricin.[29] A number of

phosphonous acid analogues of naturally occurring amino acids have been synthesised.[30] Several of these compounds showed moderate to good antibiotic activity *in vitro*. The most active compounds were the analogues of *L*-alanine, *L*-valine and *L*-methionine.[30]

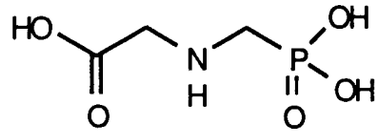


(19) (20)

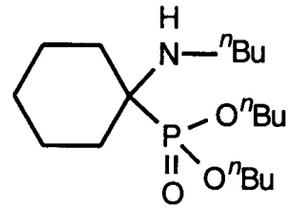
Figure 1.7: Naturally Occurring Aminophosphonous Acids

1.1.2. Plant Growth Regulatory Aminophosphonic Acids

Glyphosate, (*N*-phosphonomethyl)glycine (Figure 1.8) **(21)** is best known under Monsanto's trade name *Roundup*, which is now marketed in more than 100 countries. Glyphosate has been shown to elicit its herbicidal properties *via* inhibition of 5-enolpyruvylshikimate-3-phosphate synthase, thus blocking the shikimate pathway.[31] The lead provided by the structure of (*N*-phosphonomethyl)glycine **(21)** has been explored exhaustively. However, information on the structures and activities of these analogues is presented almost exclusively in the patent literature and little is recorded about the structure-activity relationships.[12] One other amino phosphonic acid derivative with herbicidal properties is the compound di-*n*-butyl 1-(*N*-*n*-butylamino)cyclohexylphosphonate **(22)** which is licensed for use in Germany under the tradename *Trakephon*. The mechanism of action of this compound is not clear, although it appears to disrupt the integrity of the plant cell membrane.[12]



(21)



(22)

Figure 1.8: Commercial Herbicidal Phosphonic Amino Acid Derivatives

The antibacterial compound phosphinothricin **(12)** also has important herbicidal activity.[21] The monoammonium salt of phosphinothricin (glufosinate-ammonium) is an active ingredient of *Basta*, Hoechst's herbicide which is marketed in Europe and Japan. It appears that its mechanism of herbicidal activity is the same as that of its antibacterial action, that is it inhibits glutamine synthase so that plants treated with it rapidly accumulate toxic levels of ammonia.[12] The phosphonous acid analogue **(20)** of phosphinothricin also shows interesting plant growth inhibiting properties.[30]

The unusual, naturally occurring amino acid 3,4-didehydro-5-phosphono-*D*-norvaline is found in the antibacterial phosphonopeptides plumbeomycins **(13)**. This aminophosphonic acid has been shown to have pronounced herbicidal activity, with high selectivity towards monocotyledons.[32]

1.1.3. Anticancer Activity of Phosphonic Amino Acids

Some analogues of phosphinothricin have been shown to have anti-tumour properties (Figure 1.9). The phospha^c-peptides **(23 & 24)** have both been shown to inhibit the growth of the experimental tumour L1210 in mice.[27] The cyclic analogue of phosphinothricin **(25)** and an analogue **(26)** of the tripeptide Bialaphos, incorporating this cyclic amino acid have also been shown to have anti-cancer properties. Interestingly, all these compounds exhibit very low herbicidal activity, unlike other phosphinothricin derived

compounds. Little information is available about the anticancer activities, but both compounds were active against the tumour cell lines L-1210 and S180-ascides in mice.[15] It is also reported that all these compounds have low toxicity, especially the phospholane amino acid. The azaphosphorinane **(27)**, a cyclic analogue of norvaline, has also been shown to have pronounced antitumour activity. However, unlike the phosphinic acid derivatives it also shows a high toxicity.[32]

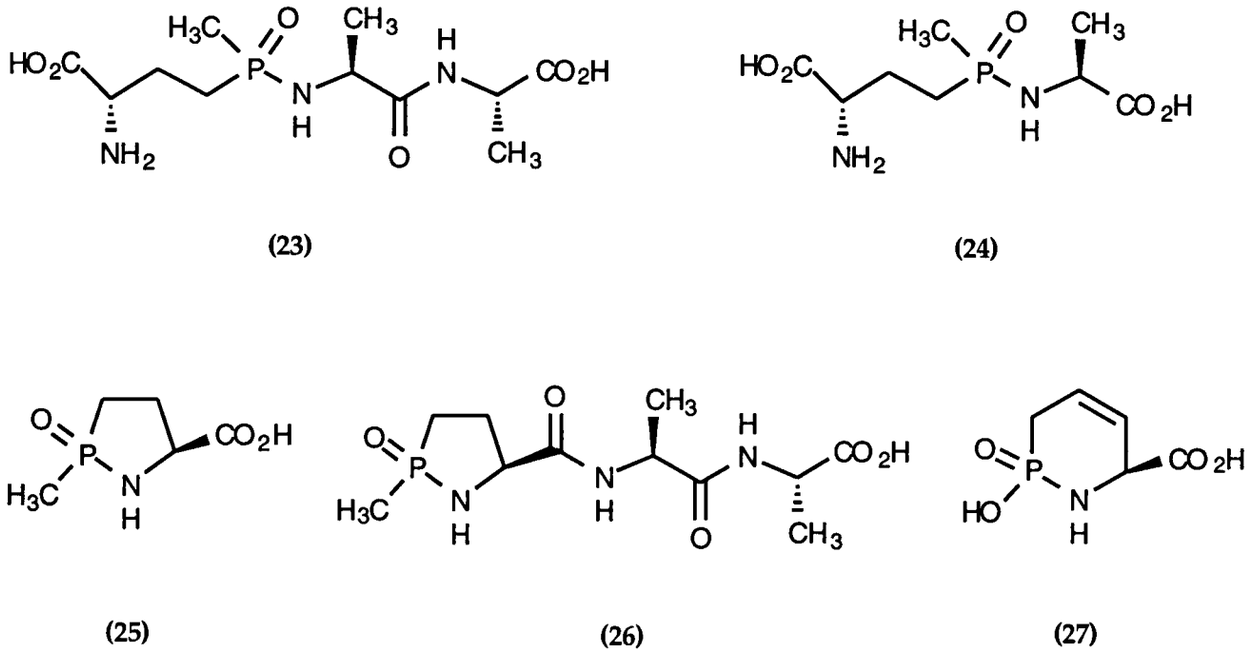


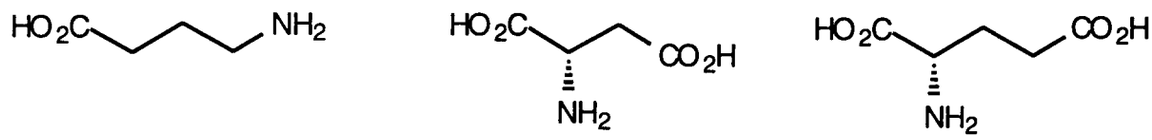
Figure 1.9: Anticancer Phosphonic Amino Acid Derivatives and Phosphonopeptides

Aminoalkanephosphonic acids and the related aminophosphinic and aminophosphonous acids are found throughout nature and they have been shown to have a wide range of biological activities. Since the discovery of their biological activities, phosphonic acid analogues of almost all the proteinergic amino acids have been synthesised.[30] Because of the well recognised involvement of various amino acids in neurotransmission processes, it is not surprising that aminophosphonates are also among the various amino acid analogues examined for neurophysiological activities. Aminophosphonic acids are now recognised as extremely important neuroactive compounds that have

played a significant role in the development of understanding of excitatory amino acid neurotransmission.

1.2. Excitatory Amino Acid Neurotransmitters

Amino acids (Figure 1.10) play an intimate role in neurotransmission processes in the mammalian central nervous system (CNS). γ-Aminobutyric acid (GABA) **(28)** and its analogues have inhibitory actions mediated *via* two distinct receptor types termed GABA-A and GABA-B. The excitatory amino acids *L*-aspartic acid **(29)** and *L*-glutamic acid **(30)** have been shown to mediate their actions *via* several distinct classes of excitatory amino acid (EAA) receptors, known as NMDA, AMPA, kainate, AP4 and metabotropic sub-types.



(28) **(29)** **(30)**

Figure 1.10: Endogenous Neuroactive Amino Acids

1.2.1. Physiological and Pathophysiological Functions of EAA Receptors

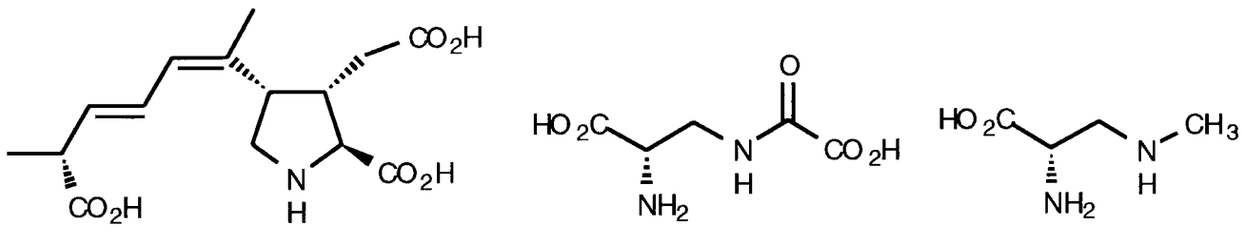
EAA receptors are now accepted to be the main transmitter receptors mediating synaptic excitation in the mammalian CNS. They are involved with many physiological phenomena, ranging from the processing of sensory information through coordinated movement patterns to cognitive processes, learning and memory.[33, 34] Dysfunction of these systems leads to various neurological disorders including memory disorders, epilepsy and spasticity. There is also considerable evidence to indicate that EAA receptors play a role in neurodegenerative conditions such as those associated with Huntington's disease, stroke, schizophrenia and Alzheimer's disease.[35]

A number of neurological disorders are characterised by excitatory amino acid neuronal degeneration and excitotoxicity due to hyperactivation of EAA receptors may be involved in the aetiology of these diseases. Strong evidence for the involvement of excitatory amino acids in these disorders arises from the fact that administration of excitatory amino acids to animals induce similar patterns of neurodegeneration to those observed in human neurodegenerative disorders. The fact that administration of excitatory amino acid antagonists can block these effects also indicates that these receptors play an important role in these diseases.

Neuronal loss after ischaemia, arising from stroke, hypoxia and hypoglycemia also appears to be due to an excitotoxic mechanism mediated by hyperstimulation of excitatory amino acid receptors. These energy deficient states cause an extracellular increase in concentrations of *L*-aspartic **(29)** and *L*-glutamic **(30)** acids, resulting in the neurons literally being excited to death. The brain damage that results from these conditions occurs mainly in regions with prominent excitatory systems and, in animal models, can be prevented to a large degree by the administration of certain excitatory amino acid receptor antagonists.[35]

One syndrome characterised by acute neurodegeneration arises due to poisoning by domoic acid (Figure 1.11) **(31)**. It is probably induced by selective activation of kainate receptors. Domoic acid is produced by the marine algae *Psuedo-nitzchia australis* and can be consumed in toxic quantities by people eating mussels that have fed on the algae. An outbreak of domoic acid poisoning occurred in western Canada in 1987. Symptoms arose a few hours after ingestion of the mussels and included acute sensorimotor disturbances and in some cases a chronic syndrome with amnesia resulted. Four of the cases were fatal and the pathology was found to be largely confined to areas of the brain with high densities of kainate receptors.[36]

Two chronic neurological syndromes have been tentatively linked to dietary consumption of amino acid toxins of plant origin. Neurolathyrism, a spastic disorder, occurring in East Africa and southern Asia is associated with the consumption of chick peas, a staple food in times of drought. The toxin has been identified as β-*N*-oxalylamino-*L*-alanine (BOAA) **(32)**, which behaves as a glutamate-like excitant principally at AMPA receptors. The Chamorros living on the Pacific island of Guam show a high incidence of amyotropic lateral sclerosis (ALS), often associated with clinical signs of senile dementia. Guam disease is thought to be linked to a plant whose seeds are used to make flour. The flour contains the amino acid β-*N*-methyl-amino-*L*-alanine (BMAA) **(33)**, that is thought to be the exogenous excitotoxin in Guam disease. BMAA is a neutral amino acid that is not directly excitotoxic *in vitro*. However, in the presence of bicarbonate (often used in baking) it becomes excitotoxic, perhaps due to the formation of an α-methyl carbamate. The excitotoxicity of BMA **(33)** *in vitro* can be blocked by NMDA antagonists indicating an action at NMDA receptors.[35]



31 32 33

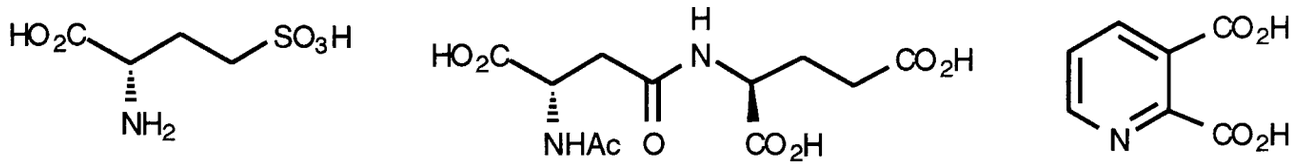
Figure 1.11: Exogenous Neurotoxins

There is a need for effective prophylaxis and therapy in acute disorders that involve excitotoxic mechanisms and in chronic neurodegenerative disorders. Thus, excitatory amino acid receptor agonists and antagonists are of major interest as both experimental tools and as potential drugs for the treatment for CNS disorders.

1.3. EAA Receptor Pharmacology

It is now 40 years since the convulsant effects of *L*-aspartic acid **(29)** and *L*-glutamic acid **(30)** were first reported.[37] Since that time a wide array of electrophysiological, biochemical, pharmacological and anatomical studies have been carried out using excitatory amino acids. Although the development of selective agonists and antagonists has led to an increased understanding of EAA receptors, the identification of an endogenous neurotransmitter has proved more difficult.

Both *L*-aspartic acid **(29)** and *L*-glutamic acid **(30)** are present in the CNS and both have the ability to cause excitatory responses at EAA receptors. However, the ubiquity of *L*-glutamic acid in the brain and its involvement in both protein synthesis, nitrogen metabolism and finally its role as a precursor of the inhibitory neurotransmitter GABA **(28)** makes studies of its function as a neurotransmitter very complicated.[38] Considerable evidence has led to the proposal that *L*-aspartic acid **(29)** and probably also *L*-glutamic acid **(30)** are both endogenous neurotransmitters in the mammalian CNS.[39] The most likely scenario is that each of these compounds acts as the endogenous neurotransmitter on different populations of receptors.[33] However, three agents (Figure 1.12) other than *L*-aspartic acid **(29)** and *L*-glutamic acid **(30)** have also been postulated as transmitter candidates for synapses mediated by excitatory amino acid receptors; homocysteaic acid **(34)**, *N*-acetylaspartylglutamic acid (NAAG) **(35)** and quinolinic acid **(36)**. All these compounds fulfil many of the criteria for an endogenous neurotransmitter and it is possible that some or all of these compounds may act at different receptor populations.[40]



(34) (35) (36)

Figure 1.12: Possible Candidates for an Endogenous EAA Neurotransmitter

1.3.1. Receptor Characterisation

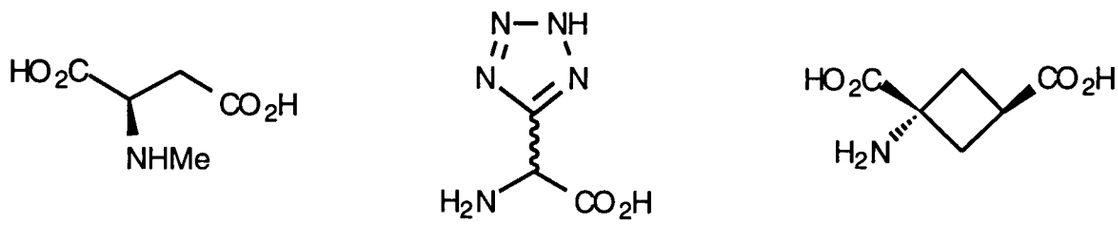
As both *L*-aspartic acid **(29)** and *L*-glutamic acid **(30)** are both flexible molecules capable of existing in a multitude of conformations. This is probably a major factor in their ability to activate a range of different EAA receptors. However, this makes them rather poor tools for the understanding of these receptors. The classification of EAA receptor sub-types has, therefore, relied on the development of potent and selective exogenous compounds. Initial studies utilising a variety of agonists and antagonists of excitatory neurotransmission indicated that at least three ionotropic receptor systems mediate the actions of excitatory amino acids, NMDA, AMPA and kainate receptor types, all of which are linked to ion channels. More recently, two other receptor classes have been identified. The AP4 receptor type and the 'metabotropic receptor' have both been recognised as having actions linked to adenylate cyclase activity and the metabolism of phosphonoinositol respectively.[41, 42]

1.4. Excitatory Amino Acid Receptor Sub-types

1.4.1. NMDA Receptor

The NMDA receptor is named after the first potent and selective agonist, *N*-methyl-*D*-aspartic acid **(37)**, known for this receptor type. Several very potent and selective agonists for this receptor type have now been

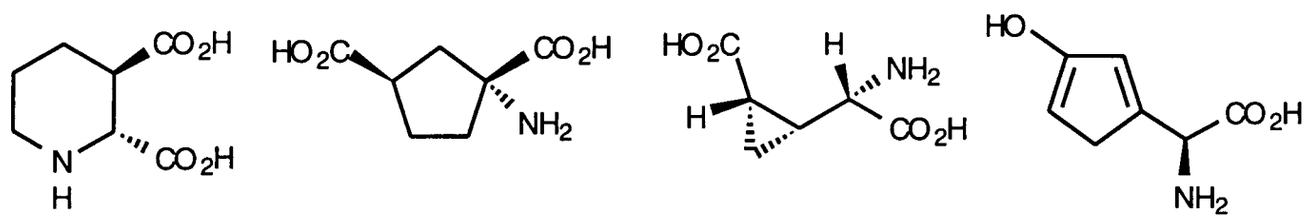
discovered (Figure 1.13). Two of the most potent known agonists are *D,L*-(tetrazol-5-yl)glycine[43] **(38)** and (*E*-1-aminocyclobutane-1,3-dicarboxylic acid (*E*-ACBD) **(39)**, which is 20 times more potent than NMDA.[44] The Z-isomer of this compound, a natural product found in the seeds of *Ateleia herbert smithii* Pittier,[45] shows only one third the potency of NMDA.



(37) **(38)** **(39)**

Figure 1.13: Potent and Selective Agonists at the NMDA Receptor

The conformationally restrained *trans*-ACBD **(39)** and other less potent, but selective, conformationally restrained NMDA agonists (Figure 1.14) such as (2*R*,3*R*)-*trans*-2,3-piperidinedicarboxylic acid (*trans*-PDA) **(40)**, (1*R*,3*R*)-1-amino-cyclopentane-1,3-dicarboxylic acid (1*R*,3*R*-ACPD) **(41)**, (2*S*,3*R*,4*S*)-α-(carboxy-cyclopropyl)glycine ((2*S*,3*R*,4*S*)-CCG) **(42)** and ibotenic acid **(43)** are held in a 'folded' conformation. This suggests that the active conformation of glutamic acid at the NMDA receptor may be a folded one.[46, 47]



(40) **(41)** **(42)** **(43)**

Figure 1.14: Conformationally Restrained NMDA Agonists

The finding that a racemic mixture of α-amino adipate (α-AA), the next higher homologue of glutamic acid, possessed an inhibitory action against the amino acid induced excitations, marked the starting point in the search for NMDA receptor antagonists (Figure 1.15). *D*-α-Aminoadipate **(44)** was identified as the first competitive antagonist at NMDA receptors.[48]

Isosteric replacement of the ω-carboxylate group of the amino acid by other functionalities resulted in the finding that some compounds in which the ω-carboxylate group was replaced by a phosphonic acid moiety showed a very potent inhibitory action.[48] Further investigation identified *D*-2-amino-5-phosphonopentanoic acid (*D*-AP5) **(45)** and *D*-2-amino-7-phosphonoheptanoic acid (*D*-AP7) **(46)** as metabolically stable, potent and highly selective antagonists at the NMDA receptor.[49, 50] Interestingly, neither, 2-amino-4-phosphonobutanoic acid (AP4) or 2-amino-6-phosphonohexanoic acid (AP6) were found to show any inhibitory action at this receptor type.[39] More recently, the first succesful attempt to replace the α-amino acid moiety of a glutamate antagonist has been reported. A 3,4-diamino-3-cyclobutene-1,2-dione **(47)** functionality was successfully utilised as the α-amino acid isostere, resulting in a highly selective, systemically active NMDA receptor antagonist.[51] Incorporation of a ketone functionality into the carbon backbone of AP5 afforded (*R*)-4-oxo-5-phosphononorvaline **(48)**, an orally active NMDA antagonist with increased potency relative to AP5.[52]

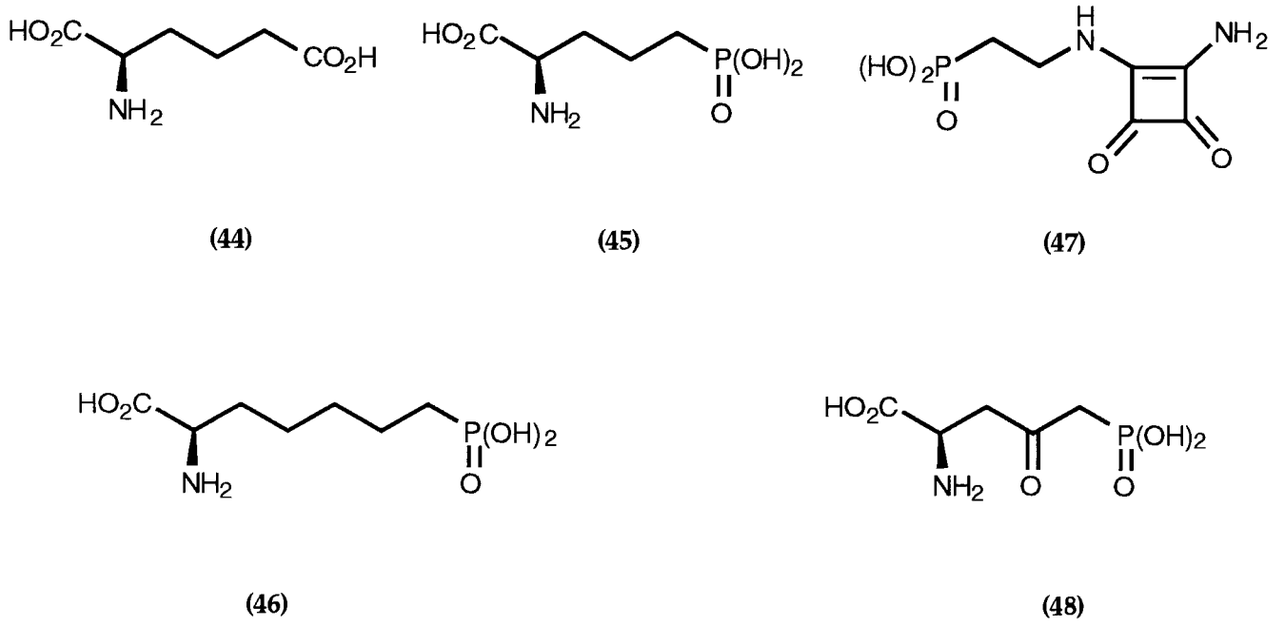
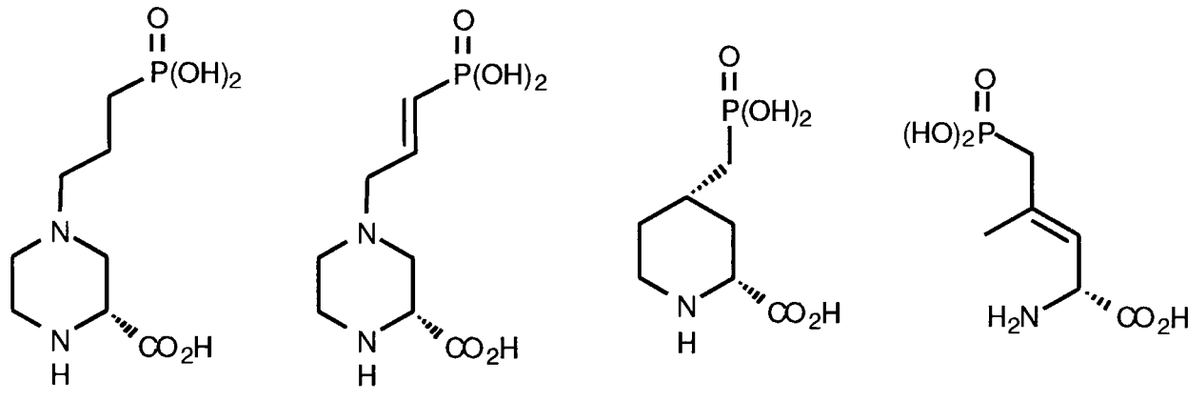


Figure 1.15: Competitive NMDA Receptor Antagonists

Once again, all these compounds are flexible molecules and give only a limited indication of the structure of the receptor site. Further exploration of these leads provided a series of structurally restricted analogues (Figure 1.16). These rigid analogues of AP7 i.e., 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) **(49)**, and 3-(2-carboxypiperazin-4-yl)propenyl-1-phosphonic acid (CPPene) **(50)** and AP5, that is *cis*-4-phosphonomethyl-2-piperidine carboxylic acid (CGS 19755) **(51)** and (*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP 37849) **(52)** respectively, are more active *in vitro* than their parent compounds. Indeed CPPene is the most potent known NMDA antagonist.[53, 54]



(49) (50) (51) (52)

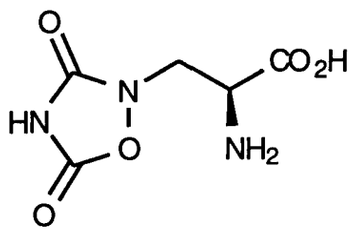
Figure 1.16: Conformationally Restrained NMDA Antagonists

Many other similar compounds have been prepared and their activity at this receptor type investigated, allowing detailed stucture activity studies to be undertaken in conjunction with molecular modelling.[55-58] However, the exact details of antagonist binding at NMDA receptors are still not fully understood. In general there are three structural features seen in antagonists of the NMDA receptor: with the exception of the achiral cyclobutenedione compound **(47)**, they all are α-amino acids that possess the *D* configuration; secondly the chain length that separates the α-acidic function and the ω-acidic side chain moiety is either four or six atoms and thirdly making the ω-acidic side chain functionality a phosphonic acid group greatly increases the potency.[47] The increased chain length of antagonists, relative to glutamic acid, and the fact that the most potent conformationally restrained antagonists are fixed in an extended chain form, indicate that the ω-acidic side-chain functionality of antagonists may bind to a different site on the receptor than the ω-acidic side-chain functionality of agonists, whilst the amino and α-acidic functionalities bind to the same site in both cases.[33] Another possibility is that agonists and antagonists bind to the same sites on the receptor but the binding of antagonists results in the receptor undertaking a different conformation to that which agonists bind to.[33] Initially it was suggested that different antagonists may bind to different sites on the receptor. For example, the

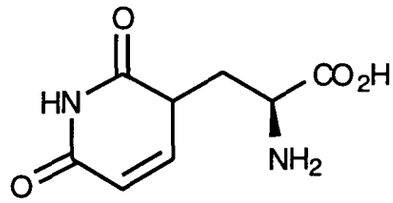
phosphonic acid group of AP5 may bind to a different site than the phosphonic acid group of AP7.[55] However, further study has indicated that this is unlikely and that there appears to be only one binding site for antagonists.[59]

1.4.2. AMPA Receptor

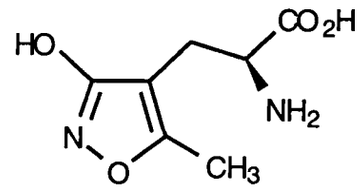
Willardine (Figure 1.17) **(53)** and quisqualic acid **(54)** were the first two agonists shown to be selective at the AMPA-type receptor. In fact, AMPA-type receptors were initially classified as quisqualate-type receptors until recent studies showed that quisqualic acid also acts at kainate-type receptors and its structural analogue *L*-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) **(55)** is a far more selective agonist.[60]



(53)



(54)



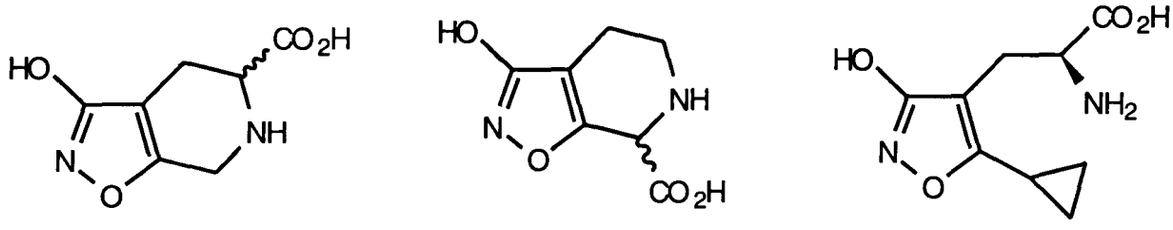
(55)

Figure 1.17: Agonists at the AMPA Receptor

The isoxazole group of compounds allows comparisons to be made, in particular between the requirements for activation of the NMDA receptor and those for activation of the AMPA receptor. The highly conformationally restricted analogues of AMPA (Figure 1.18), (*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo [5,4-*c*]pyridine-5-carboxylic acid (5-HPCA) **(56)** and the related compound (*RS*)-3-hydroxy-4,5,6,7-tetrahydroisoxazolo [5,4-*c*]pyridine-7-carboxylic acid (7-HPCA) **(57)**, a similarly immobilised analogue of AMPA, are both potent and selective agonists at this receptor sub-type.[33] In

comparison the relatively flexible (cf 5-HPCA and 7-HPCA) 3-isoxazole bioisostere of glutamate, ibotenic acid **(43)** is a potent NMDA agonist.[33]

The conformational similarity between 7-HPCA and 5-HPCA has been confirmed by x-ray crystallography and ^{1}H-nmr spectroscopy. Both compounds are planar, with the carboxyl group in the axial and equatorial positions respectively. This fact, as well as their virtually identical pharmacological profiles, has resulted in the suggestion that these compounds represent the active conformations of AMPA and glutamic acid **(30)** at AMPA-type receptors.[33] It is also recognised that AMPA-type receptors are capable of accommodating bulky substituents of agonist molecules.[39] This has been confirmed by the recent report that (*RS*)-2-amino-3-(5-cyclopropyl-3-hydroxyisoxazol-4-yl)propionic acid **(58)**, a cyclopropyl substitited analogue of AMPA, is equipotent with AMPA itself as an agonist.[61]

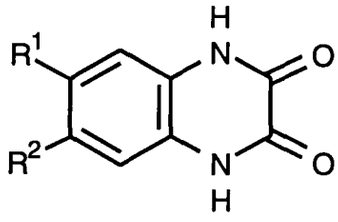


(56) **(57)** **(58)**

Figure 1.18: Structurally Restrained and Sterically Hindered AMPA Agonists

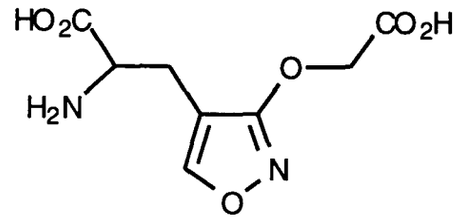
Until recently, potent and selective antagonists for the AMPA-type receptor were unavailable. However, two quinoxalinediones (Figure 1.19), 6,7-dinitroquinoxaline-2,3-dione (DNQX) **(59)** and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) **(60)**, have been shown to be potent competitive antagonists at non-NMDA-type receptors. These two compounds act predominantly at AMPA receptors but also show weak activity at kainate-type receptors.[62] Centrally administered CNQX **(60)** reduced knee joint inflamation and

behaviour manifestations of arthritis in rats suggesting a role for central AMPA receptors in the development of peripheral joint inflammation.[63] The AMPA analogue, (*R S*)-2-amino-3-[3-carboxymethyl-5-methylisoxazol-4-yl]propionic acid (AMOA) **(61)** has also been found to competitively inhibit AMPA **(55)** induced excitations whilst showing only a slight effect on excitations mediated by NMDA **(37)** and kainate.[62] A series of 2-phosphonoethylphenylalanines have been prepared and their activity investigated, 2-phosphonoethyl-(5-methyl)phenylalanine **(62)** was found to be the most potent of this series.[63]

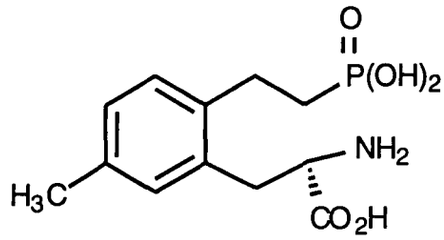


(59) DNQX $R^1=NO_2\ R^2=NO_2$

(60) CNQX $R^1=NO_2\ R^2=CN$



(61)



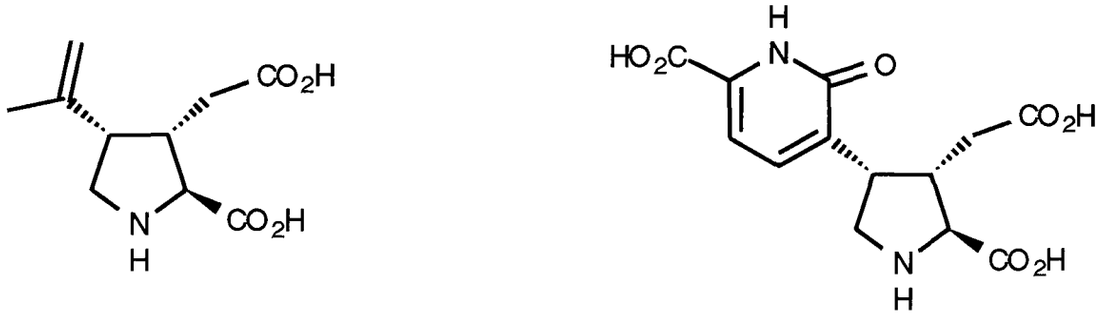
(62)

Figure 1.19: Competitive Antagonists at the AMPA Receptor

1.4.3. Kainate Receptor

The prototypic agonist at this kainate type receptors is the compound α-kainic acid (Figure 1.20) **(63)**, a neurotoxin from the seaweed *Digena simplex*. Two other pyrrolidine amino acids, domoic acid **(31)** and acromelic acid **(64)**, are even more potent than kainic acid as neuroexcitants. This receptor-type exhibits a high degree of stereoselectivity, the β-isomer, with the 2-carboxyl

group in the opposite configuration, being inactive. It also appears that an unsaturated side chain at the 4-position, although not essential, is preferable. A common structural feature of kainate receptor agonists is the presence of a π-electron system in the molecule. This unsaturated moiety appears to be advantageous for interactions with kainate receptors, with the extended conjugation in domoic acid and acromelic acid resulting in even more potent excitatory effects than observed with kainic acid. However, the unsaturated moiety is not an absolute requirement, with 3 out of the 4 stereoisomers of 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) showing weak action at this receptor type.[39]

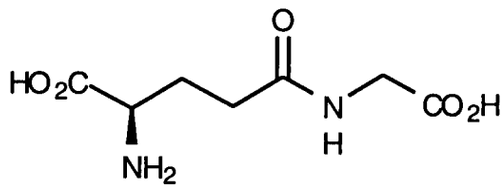


(63) **(64)**

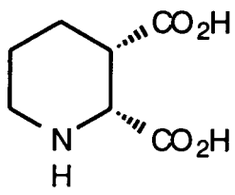
Figure 1.20: Agonists at the Kainic Acid Receptor Sub-type

As in the case of AMPA-type receptors, the lack of potent and selective antagonists for the kainate type receptor has hindered further classification of this class of receptors. Two compounds known to act preferentially as NMDA antagonists also block responses to kainic acid: the two compounds are the dipeptide γ-*D*-glutamylglycine (γ-DGG) (Figure 1.21) **(65)** and *cis*-2,3-piperidine dicarboxylic acid (*cis*-2,3-PDA) **(66)**.[48, 64] More recently, the AMPA dimer (*RS*)-2-amino-3-[2-[3-methyl-3-oxoisoxazolin-4-yl)-methyl]-5-methyl-3-oxoisoxazolin-4-yl]-propionic acid (AMNH) **(67)** has been reported to be a selective kainate-type antagonist.[65]

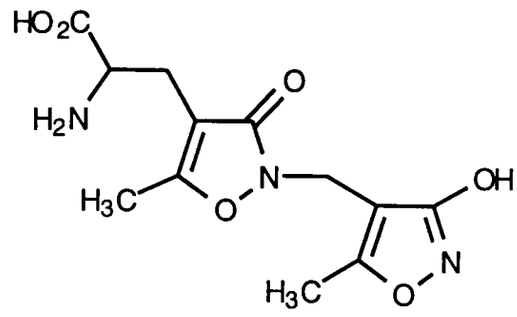
In all cases where both enantiomers of compounds that show antagonist activity at the kainate recptor are available, the *D*-isomer shows greater activity. Although the number of compounds that show potent and selective antagonist activity at this receptor is limited, and the most potent antagonist, AMNH **(67)** has not yet been prepared in an enantiomerically pure form. This may indicate that, like the NMDA receptor, the *D*-configuration at the α-carbon is necessary for antagonist activity at the kainate receptor.[65]



(65)



(66)



(67)

Figure 1.21: Competitive Antagonists at the Kainic Acid Receptor

1.4.4. AP4 Receptor

In contrast to the NMDA, AMPA and kainate receptor sub-types, which were defined through the actions of exogenous excitatory amino acids, the *L*-AP4 receptor was discovered because *L*-2-amino-4-phosphonobutanoic acid (*L*-AP4) (Figure 1.22) **(68)** appeared to be a potent antagonist at subpopulations of synaptically evoked excitatory responses.[66] Recent experiments indicate that *L*-AP4 **(68)** most probably acts as an agonist, presynaptically, causing a reduction of endogenous EAA release and thus causing an apparent inhibitory action.[39] It now appears that the AP4 receptor

is not in fact ionotropic as first thought, but is fact a sub-class the of metabotropic receptor which is linked to adenylate cyclase activation.[42]

The ω-phosphonic acid analogue of glutamic acid *L*-AP4 **(68)** has now been reported independently by several groups to inhibit synaptic responses in several different neuronal systems. The inhibition was selective for *L*-AP4 **(68)** as the *D*-isomer and a variety of related compounds were found to be inactive in these systems. These findings led to the classification of a the AP4-type receptor.[47] *L*-Serine-*O*-phosphonic acid **(69)** was found to mimic the inhibitory effects of *L*-AP4, indicating that is was also active at this site.[39]

It now appears that there are at least three distinct AP4 binding sites in the CNS. Two quisqualic acid-sensitive sites are found in the medial perforant path and a third site in the lateral perforant path that is insensitive to quisqualic acid. The quis-sensitive sites were discovered when it was shown that brief exposure of rat hippocampal slices to quisqualic acid **(54)** sensitised these neurons to depolarisation by a number of compounds. The potency of some compounds, including *L*-AP4, *L*-AP5, phosphinothricin **(12)** which is the phosphinic acid analogue of AP4 and *Z*-3-amino-3-carboxy-cyclopentylphosphonic acid (*Z*-ACPP) **(70)** increased more than four-fold after exposure to quisqualic acid. This sensitisation can be reversed by exposure to *L*-α-aminoadipate (*L*-α-AA). The two separate quis-sensitive sites are now distinguished by the action of *L*-2-amino-6-phosphonohexanoic acid (*L*-AP6) **(71)**, which is a potent and selective agonist at one of the quis-sensitive sites. The second quis-sensitive site appears to be activated by *L*-AP4 **(68)** but not by *L*-AP6 **(71)**. The third site is activated by *L*-AP4 but is insensitive to quisqualic acid.[67]

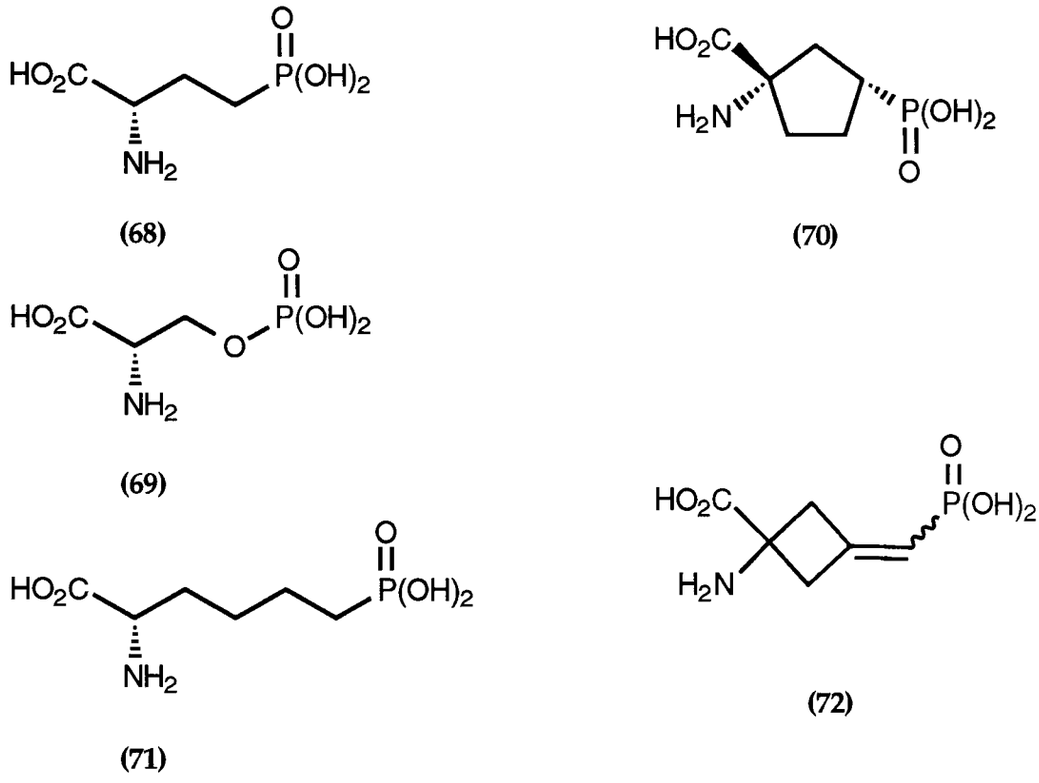


Figure 1.22: Compounds that Act at the AP4 Receptor

As the spectrum of activity of *Z*-ACPP **(70)** closely resembles that of *L*-AP4 in the medial perforant path, it has been suggested that the quis-sensitive site, at which *L*-AP4 is active and *L*-AP6, is inactive requires a spatial arrangement of functional groups similar to that of *Z*-ACPP **(70)**.[68] Since the amino and the phosphonic acid moieties are *cis* to one another in this isomer, the possibility of ionic interaction between these two moieties exists. This would give rise to a highly folded conformation.[47] It is also thought that the presence of a primary amino group and a mono- or dicationic phosphorus group are necessary for activity at this receptor, however a carboxylic group does not appear to be a requirement as 3-aminopropanephosphonic acid shows significant activity at this site.[68]

Recently, the highly rigid and conformationally extended 1-amino-3-(phosphonomethylene)cyclobutane-1-carboxylic acid **(72)** was shown to inhibit evoked responses in the rat lateral perforant pathway, suggesting that the *L*-AP4 **(68)** assumes an extended conformation at quis-insensitive AP4 receptors.[69]

L-AP4 **(68)** assumes an extended conformation at quis-insensitive AP4 receptors.[69]

There are clearly three distinct sub-classes of AP4 receptors, two quis-sensitive sites; one at which *L*-AP4 **(68)** is more active and one at which *L*-AP6 **(71)** is specific. This suggesting that *L*-AP4 **(68)** binds in a folded conformation at one and an extended conformation at the other site. The third receptor is activated by *L*-AP4 **(68)** but is not sensitised to quisqualic acid. However, there is still little detailed information about the binding sites of these different sub-populations of AP4 receptors in the central nervous system. Clearly, further investigation of stucture-activity relationships is required.

1.4.5. Metabotropic Receptor

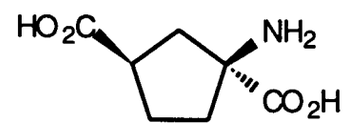
The ionotropic (NMDA, AMPA and Kainate) EAA receptors are directly linked to the influx of sodium and calcium ions into the target cell. In contrast, metabotropic receptors are G protein linked to activation of inositol specific phospholipase C and the hydrolysis of phosphoinositides to form intracellular second messengers (IP_3 and diacylglycerol). This different receptor mechanism, when compared to that of ionotropic receptors, suggests that the functional role and potential utility of pharmacological agents acting at metabotropic EAA receptors may be unique. The pharmacological properties of this receptor indicate that it is distinct from previously described receptors, in that quisqualic acid, ibotenic acid and glutamic acid are potent agonists and NMDA, AMPA and kainic acid are not.[66]

Molecular cloning techniques have revealed the existence of at least seven sub-classes of metabotropic receptor ($mGlu_1$-$mGlu_7$) that can be divided into three general classes on the basis of sequence similarity: $mGlu_1$ and $mGlu_5$, which are linked to through phosphoinositide specific phospholipase to phosphoinositide hydrolysis and intracellular Ca^+ mobilisation; $mGlu_2$ and

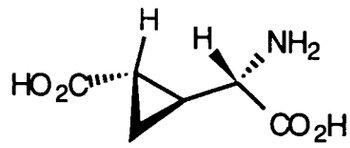
formation; and $mGlu_4$, $mGlu_6$ and $mGlu_7$ also negatively linked to adenylate cyclase activity, this third class is the AP4-type receptor described above.

Initially, this receptor type was only distinguished from ionotropic receptors by the nature of its second messenger system - phosphoinositol hydrolysis. The compound (1*S*,3*R*)-1-amino-1,3-cyclopentanedicarboxylic acid ((1*S*,3*S*)-ACPD) (Figure 1.23) **(73)** was found to be a selective agonist and allowed this receptor to be distinguished pharmacologically.[70] This was followed by the discovery that the conformationally restricted analogue of glutamic acid, (2*S*, 3*S*, 4*S*)-α-(carboxycyclopropyl)glycine ((2*S*,3*S*,4*S*)-CPG) **(74)**, is even more potent than (1*S*,3*S*)-ACPD **(73)** in stimulating phosphoinositol hydrolysis in the rat hippocampus.[71] *trans*-Azetidine-2,4-dicarboxylic acid **(75)** is a selective agonist which stimulates phosphoinositol hydrolysis in rat cerebral granular cells.[63]

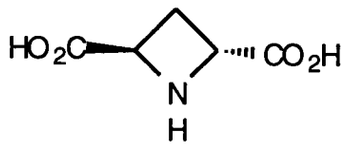
Quisqualic acid **(54)** and ibotenic acid **(43)** were the first agonists described for this receptor type, but neither of these is selective and both compounds appear to act as partial agonists rather than full agonists.[72] However, quisqualic acid is one of the most potent agonists known for these receptors.



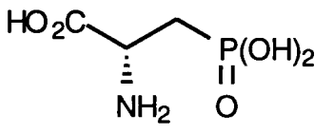
(73)



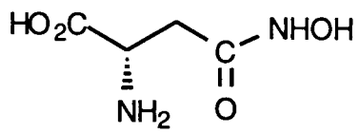
(74)



(75)



(76)



(77)

Figure 1.23: Compounds that Act at Metabotropic Receptors

Both *L*-2-amino-3-phosphonopropanoic acid (AP3)[73] **(76)** and *L*-AP4 **(68)** are known to have antagonist activity at metabotropic EAA receptors. *L*-AP3 **(76)** has greater selectivity and potency for metabotropic receptors than ionotropic receptors and *L*-AP4 is inactive in many preparations from immature sources, indicating that these receptors may be involved in developmental processes. *L*-Aspartate-β-hydroxamate (*L*-asp-β-HA) **(77)** has been found to act as an antagonist of ibotentate stimulated phosphonoinositol hydrolysis. However, it does not appear to be competitive or reversible. *L*-AP3 **(76)** blocks responses to quisqalic acid **(54)**, ibotenic acid **(43)** and (1*S*,3*S*)-ACPD) **(73)** to the same degree, whereas *L*-AP4 appears to antagonise ibotenate induced responses to a greater extent than those induced by quisqualate.[72] *D*-Aspartate induced responses are not antagonised by *L*-AP3 **(76)** or *L*-asp-β-HA **(77)**.[74] Both *L*-SOP **(69)** and NAAG **(35)** have been shown to selectively activate metabotropic receptors which are negatively coupled to andenyl cyclase.[63] Both ((1*S*,3*S*)-ACPD) **(73)** and ((2*S*,3*S*,4*S*)-CPG) **(74)** show

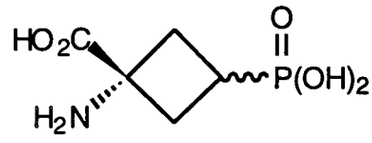
some selectivity for $mGlu_2$ and $mGlu_3$ receptors.[42] Thus judicious use of agonists can be used to explore the subgroups of metabotropic receptors.

1.5. Cyclic Analogues of Phosphonic Amino Acids in EAA Pharmacology

Since the endogenous excitatory amino acids are extremely flexible molecules, use has been made of structurally restricted analogues in an attempt to characterise the EAA receptors. An effective method of restricting the flexibility of a compound is to incorporate part of the compound into a ring structure. This has already resulted in the development of some potent and specific compounds.

One such compound, *E*-1-amino-1,3-cyclobutanedicarboxylic acid (*E*-ACBD) **(39)**, has been found to be an extremely potent NMDA agonist.[44] Many other potent and selective compounds have been developed using this strategy, For example, ACPP **(70)**, ACPD **(41)**, CPG **(42)** etc. and have been invaluable in the characterisation of excitatory amino acid receptors.

All possible isomers of the cyclopentyl and cyclohexyl analogues of AP4 have been prepared and their activity investigated. Despite the fact that *L*-AP4 **(68)** plays such an important role in the pharmacology of two receptor types (AP4 and metabotropic) and the fact that *L*-AP3 **(76)** is also active at the metabotropic receptor, indicating that the active conformation is likely to be intermediate between these two compounds, the simplest structurally restricted analogue of AP4, namely 3-amino-3-carboxycyclobutanephosphonic acid **(78)** (Figure 1.24) has yet to be prepared.

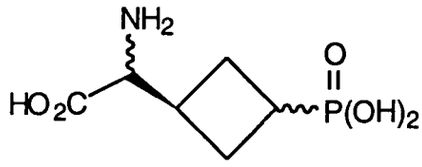


(78)

Figure 1.24: 3-Amino-3-carboxycyclobutanephosphonic acid

As there is still little information regarding the active binding conformation of *L*-AP4 **(68)** at the AP4 receptor and given that *L*-AP4 is not specific for the AP4 receptor but also interacts at the metabotropic receptor, a need for further structurally constrained compounds is apparent. More importantly, antagonists, in particular those with subtype selectivity, are required to elucidate the roles of metabotropic glutamate receptors in synaptic activity.

It has already been shown that subtle changes in the way a compound is structurally restrained can result in large changes in activity. For example, the cyclobutane analogue of glutamic acid is around 100 fold more active than the cyclopentane analogue at the NMDA receptor. Similarly, 1-amino-3-(phosphonomethylene)cyclobutanecarboxylic acid **(72)** has been prepared and has been found to act at the AP4 receptor.[68] However, the corresponding analogue (Figure 1.25) 3-(amino-carboxymethyl)cyclobutanephosphonic acid **(79)**, with the phosphonic acid group directly attached to the cyclobutane ring and the amino acid functionality removed from the ring by one carbon has not been made. Again, it would be interesting to see what effect the subtle difference in the way that this compound is constrained would have in terms of activity.



(79)

Figure 1.25: 3-(Amino-carboxymethyl)cyclobutanephosphonic Acid

1.6. Aims

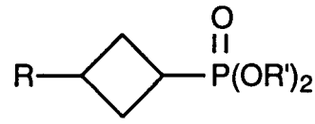
We concluded that completion of the systematic investigation of cyclobutanephosphonic acid analogues of excitatory amino acids as neurotransmitters required investigation of cyclobutanes in which the phosphonic acid group is directly attached to the cyclobutane ring. However, judging by the absence of such compounds in the literature it would appear that the methodology for their preparation is lacking. Thus, the aim of the first part of this work was to develop a method for the synthesis of a 3-substituted-cyclobutanephosphonate building block, which could be used to prepare a variety of other 3-substituted-cyclobutanephosphonates, in particular the aminocyclobutane phosphonic acids described above. The use of chemical and/or enzymatic techniques to separate the stereoisomers of the aminocyclobutanephosphonic acids was also to be investigated.

Chapter 2

Synthesis of 3-Substituted-cyclobutanephosphonates

2.1. Introduction

Cyclobutanes are versatile synthetic intermediates, whilst being undoubtedly the most difficult of the small to medium sized rings to prepare. Although procedures are available for the preparation of cyclobutane, methylenecyclobutane and 1,1-disubstituted cyclobutanes, routes to 1,3-disubstituted derivatives with functionality amenable to further elaboration are not as plentiful.[75] Those that do exist generally have a carboxylate group as one of the substituents. In particular, the synthesis of intermediates that would allow access to 3-substituted-cyclobutanephosphonates **(80)** (Figure 2.1) has not been described. These 3-substituted-cyclobutane-1-phosphonates **(80)** are of interest, not only because they can be converted into cyclobutanephosphonic acid analogues of amino acids, but also for other uses such as potential achiral spacers in synthetic nucleotides.[76]

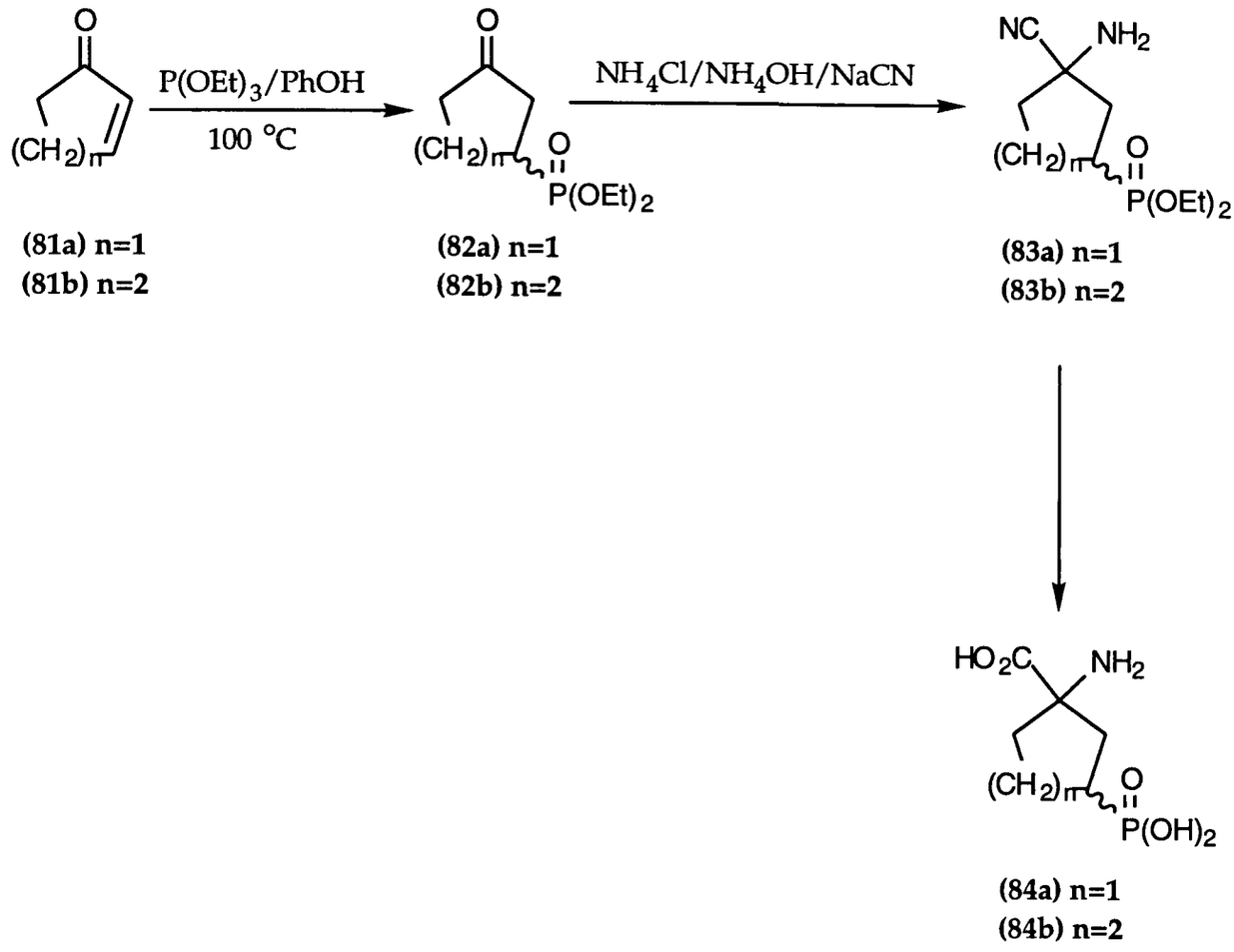


(80)

Figure 2.1: Dialkyl 3-substituted-cyclobutanephosphonate

Many related cyclopropane, cyclopentane and cyclohexane aminophosphonic acid analogues have been prepared and have subsequently provided much interesting structure-activity information.[77] The synthesis of the five **(84a)** and six membered **(84b)** ring analogues of AP4 (Figure 2.2) is

facilitated by the availability of cyclopent-2-enone **(81a)** and cyclohex-2-enone **(81b)** respectively. Treatment of these cyclic conjugated ketones **(81a-b)** with a trialkylphosphite in the presence of phenol yields the racemic 3-ketophosphonate **(82a-b)**. These intermediates are easily converted to the dialkyl 3-amino-3-cyanocyclopentane- **(83a)** or dialkyl 3-amino-3-cyanocyclohexanephosphonate **(83b)** by a Strecker reaction. Hydrolysis of the aminonitrile yields the desired aminophosphonic acids **(84)**.[77]



(81a) n=1
(81b) n=2

(82a) n=1
(82b) n=2

(83a) n=1
(83b) n=2

(84a) n=1
(84b) n=2

Figure 2.2 Synthesis of Cyclopentane and Cyclohexane Analogues of AP4

The corresponding cyclobut-2-enone is not available. Cyclopent-2-enone **(82a)** and cyclohex-2-enone **(82b)** are both stable compounds. However, cyclobut-2-enone is extremely unstable. It rapidly rearranges to the give the considerably more stable vinylketene.[78]

Related cyclopropane compounds **(87a-d)** (Figure 2.3) have been prepared by the reaction of (R)-*N*-(benzyloxycarbonyl)-allylglycine **(85)** with dimethyl diazomethylphosphonate and rhodium diacetate dimer to give an inseparable mixture of all four possible diastereoisomers of methyl 2-[*N*-[(benzyloxy)carbonyl]amino]-4,5-methano-5-(dimethylphosphono)pentanoate **(86a-d)**. Hydrolysis of the mixture of diastereoisomers afforded a mixture of the desired amino acids **(87a-d)**.[79]

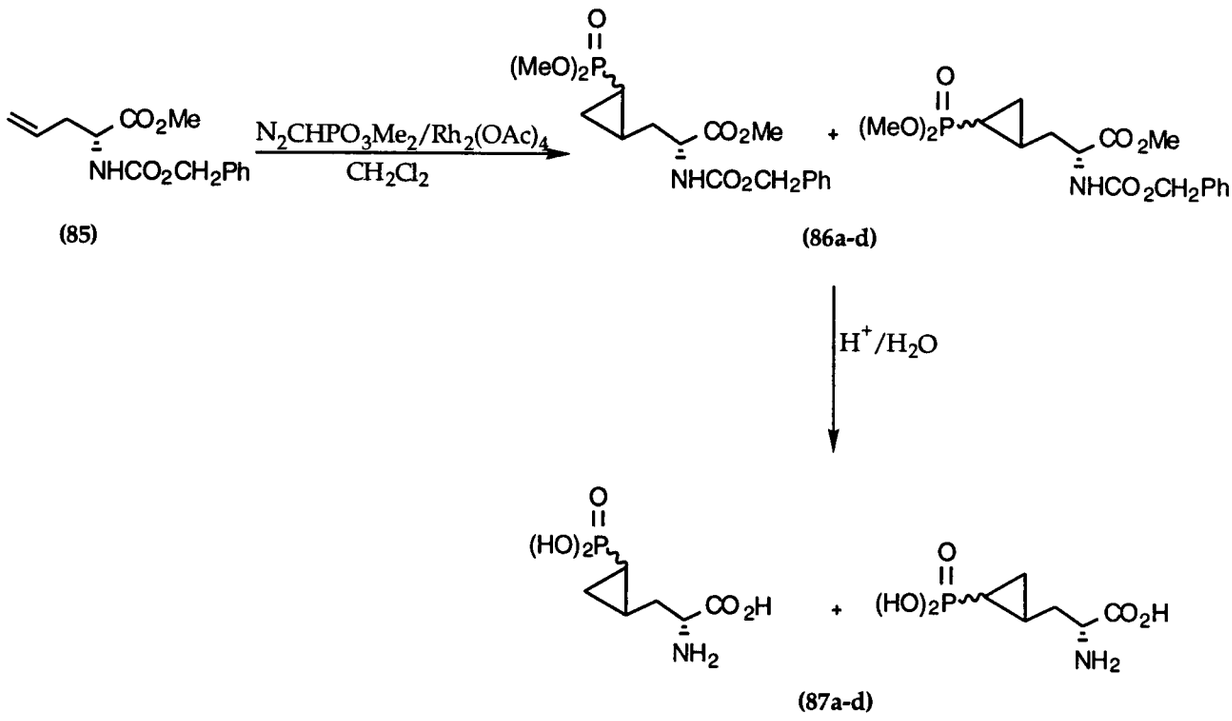


Figure 2.3: Synthesis of (E/Z)-2-Amino-4,5-methano-5-phosphonopentanoic Acid

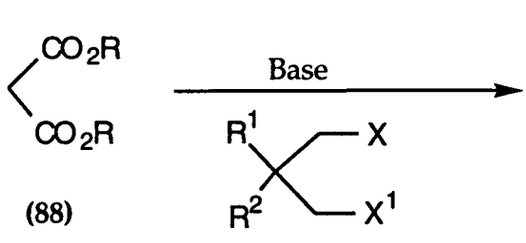
However, as this method is applicable only to the synthesis of cyclopropane rings it was unsuitable for our requirements. Two options for the synthesis of 3-substituted-cyclobutanephosphonates **(80)** were identified: either preparation of a suitably 1,3-functionalised cyclobutane by a known route, such that further transformation could introduce a phosphonate functionality, or development of the direct synthesis of a dialkyl 3-substituted-cyclobutanephosphonate **(80)**.

2.2. Discussion

Initially we decided to investigate the synthesis of cyclobutanes such as dialkyl 3-hydroxycyclobutanedicarboxylates by known synthetic methods, with subsequent conversion of this intermediate into dialkyl 3-bromocyclobutanedicarboxylates which have the potential to undergo an Arbuzov reaction to give 3-substituted-cyclobutanephosphonates **(80)**. This would provide useful intermediates, in which the carboxylic ester groups could then undergo a variety of functional group transformations furnishing a range of compounds.

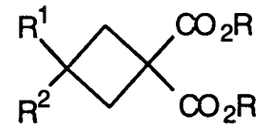
2.2.1. Malonate Synthesis of Cyclobutanes

Alkylation of a malonate ester **(88)** with a 1,3-dibromopropane **(89)** produces an alkylmalonate, intramolecular alkylation of which leads to a 1,1-disubstituted-cyclobutane **(90)** in moderate yields (Figure 2.4). This is one of the most common methods of preparing cyclobutanes. Using a suitable 2-substituted-1,3-dihalopropane allows the synthesis of 1,3-disubstituted cyclobutanes **(93)**. Avram *et al* first reported the synthesis of a 1,3-disubstituted cyclobutane **(93a)** in yields of 36 % using 1-chloro-2-benzyloxy-3-bromopropane **(91)** with sodium ethoxide as the base.[80]



(88)

(89) $R^1=R^2=H$, $X=X^1=Br$
(91) $R^1=H$, $R^2=OCH_2Ph$, $X=Br$, $X^1=Cl$
(92) $R^1=R^2=OMe$, $X=X^1=Br$

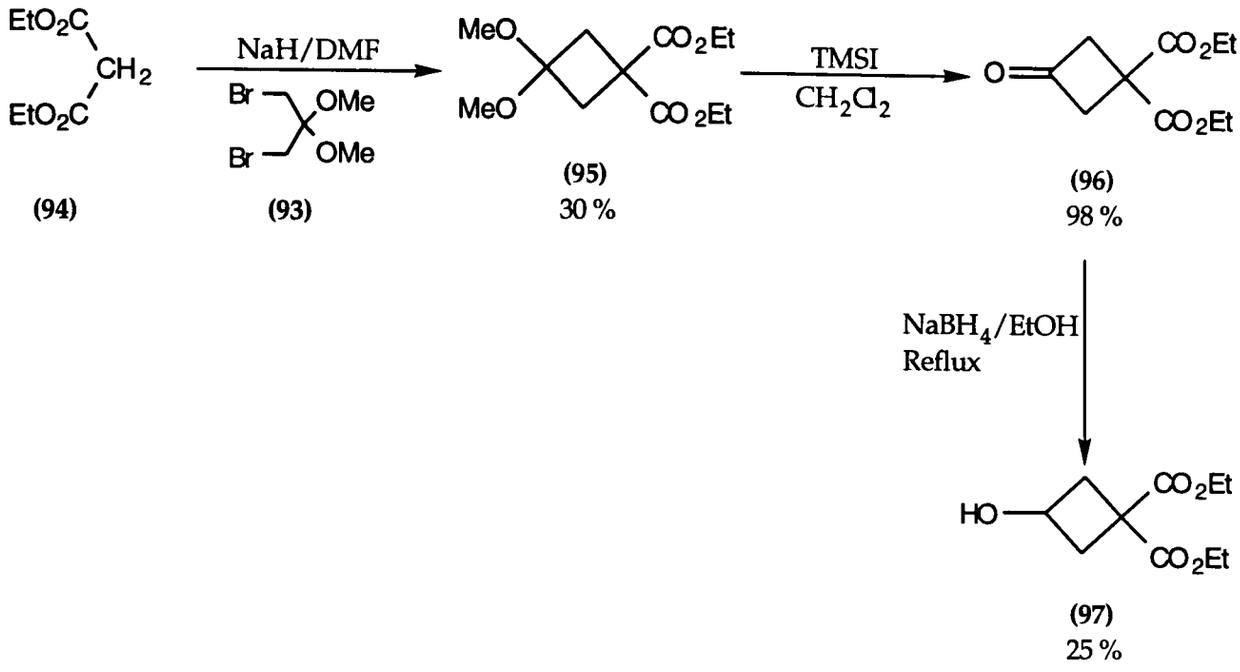


(90) $R^1=R^2=H$
(93a) $R^1=H$, $R^2=OCH_2Ph$
(93b) $R^1=R^2=OMe$,

Figure 2.4: Malonate Synthesis of Cyclobutanes

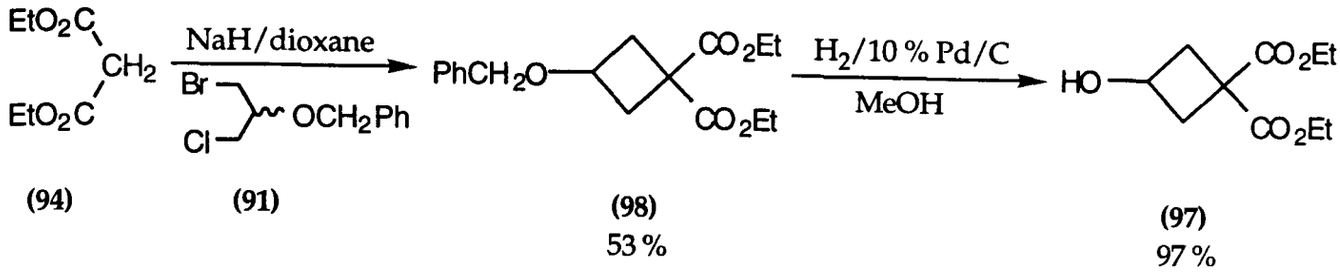
More recently, the use of 1,3-dibromo-2,2-dimethoxypropane **(92)**, which is easily prepared from acetone, methanol and bromine,[81] has been used in the synthesis of 1,3-disubstituted cyclobutanes **(93b)** (Figure 2.4). Reaction of a dialkylmalonate with 1,3-dibromo-2,2-dimethoxypropane **(92)** in the presence of sodium hydride produces the desired 1,3-disubstituted cyclobutane **(93b)**. Yields were in the range 30-56 % depending on the alkylmalonate used.[75]

As 1,3-dibromo-2,2-dimethoxypropane **(92)** is economical and easy to prepare, we decided to use this method to prepare diethyl 3-oxocyclobutanedicarboxylate **(96)** (Scheme 2.1), the reduction of which with sodium borohydride would yield diethyl 3-hydroxycyclobutanedicarboxylate **(97)** allowing subsequent conversion to a phosphonate, possibly through a 3-halocyclobutane intermediate. The synthesis of diethyl 3,3-dimethoxy-cyclobutanedicarboxylate **(95)** from 1,3-dibromo-2,2-dimethoxypropane **(92)** and diethyl malonate **(94)** in the presence of sodium hydride proceeded smoothly in 45 % yield. Deprotection of the methyl ketal **(95)** was accomplished by treatment with trimethylsilyl iodide (TMSI) in dichloromethane. The dealkylation of methyl ethers is known to proceed with selectively in the presence of esters with TMSI.[82] The reaction of TMSI was complete in 60 minutes and no evidence of any deesterified product was seen. The corresponding reaction with trimethylsilyl bromide (TMSBr) took in excess of 24 hours. The diethyl 3-oxocyclobutanedicarboxylate **(96)** was used without any further purification. Unfortunately, the sodium borohydride reduction of diethyl 3-oxocyclobutanedicarboxylate **(96)** proved problematical. At room temperature the ketone was not reduced even after extended reaction times, and at reflux in ethanol, only poor yields (< 25 %) of diethyl 3-hydroxycyclobutanedicarboxylate **(97)** were obtained.



Scheme 2.1.

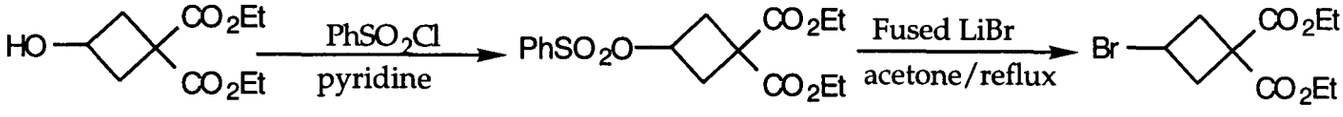
Due to the problems with reduction of the ketone functionality and as the cyclisation itself was not particularly high yielding, we decided to investigate the route described by Avram for the synthesis of diethyl 3-hydroxycyclobutanedicarboxylate **(97)** (Scheme 2.2). This route proceeds directly to the alcohol, avoiding the reduction step. 1-Chloro-2-benzyloxy-3-bromopropane **(91)** was prepared from epichlorohydrin and benzyl bromide in the presence of a catalytic amount of mercurous chloride.[80] Formation of the diethyl 3-(benzyloxy)cyclobutanedicarboxylate **(98)** proceeded smoothly using a modification of the route described by Avram, in which the alkylation was carried out with NaH in dioxane rather than using sodium ethoxide as the base.[83] The crude mixture was purified by distillation to give the cyclobutane **(98)** in 53 % yield. Hydrogenation using palladium on carbon (10 %) as a catalyst rapidly removed the benzyl protecting group, giving the alcohol **(97)** as a pale orange oil in quantitative yield.



(94) (91) (98) 53 % (97) 97 %

Scheme 2.2.

Conversion to the benzenesulfonate **(99)** was achieved quantitatively, by reaction of the alcohol **(97)** with benzenesulfonyl chloride in pyridine (Scheme 2.3). Reaction of the benzenesulfonate **(99)** with fused lithium bromide in anhydrous acetone at reflux provided the diethyl 3-bromocyclobutanedicarboxylate **(100)**, again in quantitative yield.[84] The bromocyclobutane **(100)** was purified by column chromatography. This route provided the desired diethyl 3-bromocyclobutanecarboxylate **(96)** in high overall yield.



(97) (99) 91 % (100) 95 %

Scheme 2.3.

2.2.3. Arbuzov Reaction of Diethyl 3-Bromo cyclobutanecarboxylate

The Arbuzov reaction (Figure 2.5) is one of the most versatile methods of forming carbon-phosphorus bonds and involves the reaction of an ester of trivalent phosphorus **(101)** with alkylhalides **(102)**. It is a two step reaction which results in the conversion of trivalent phosphorus in to pentavalent phosphorus. The lone pair of the electrons of the phosphite **(101)** attacks the alkyl group of the alkylhalide **(102)** to form the addition compound **(103)**, in which the alkyl group of the alkyl halide becomes attached to the phosphorus.

In the second step of the reaction, an alkyl group of the phosphite dissociates from the addition compound **(103)**, resulting in the formation of the P=O bond of the phosphonate **(104)**; the alkyl group is eliminated as a new alkyl halide **(102a)**. It is reported that the conversion of the trivalent ester linkage to the pentavalent P(=O)-C involves a net energy gain of between 32 and 65 kcal/mol in the total bond stability and acts as the driving force for the rearrangement.[85]

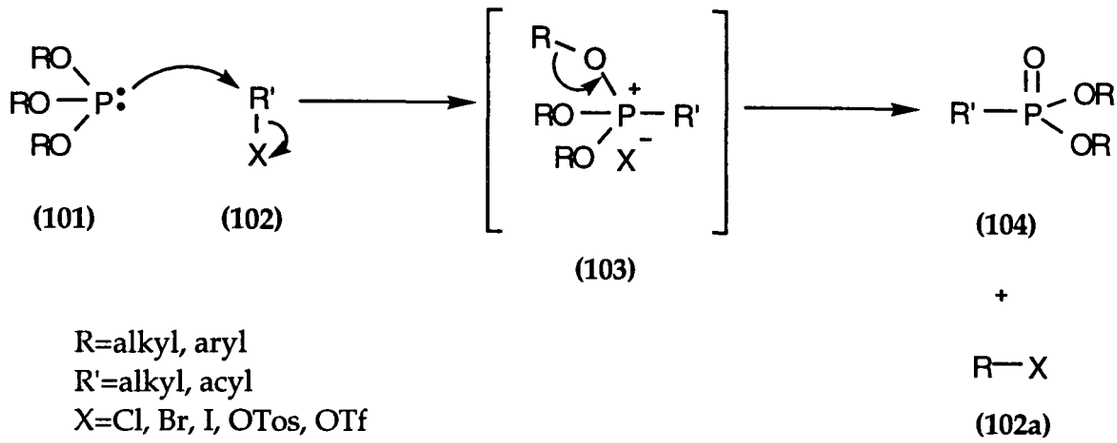


Figure 2.5: Mechanism of the Arbuzov Reaction

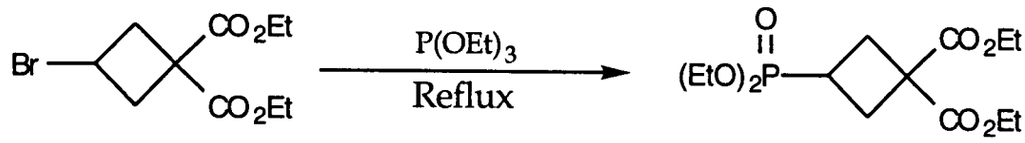
As would be expected from this mechanism, the reactivity of the alkyl halides in the Arbuzov reaction follows the usual sequence for S_N2 displacement, i.e. R(C=O)-halide > RCH_2-halide > R_2CH-halide >> RR'R''C-halide and RI > RBr > RCl. This indicates that an alkyl halide capable of reacting with nucleophilic reagents by an S_N2 mechanism is suitable as a substrate for the Arbuzov reaction. However, the majority of Arbuzov reactions have been carried out on primary alkyl halides and reaction with only a few secondary alkyl halides have been reported, for example, isopropyl iodide and ethyl α-bromopropionate.[85] One problem with the use of secondary alkyl halides as substrates is the fact that a primary alkyl halide is formed as a by-product of the reaction and this then competes with the substrate in the reaction. As a primary alkyl halide reacts faster than a

secondary alkyl halide this must be removed from the reaction mixture to allow the desired reaction to occur. Following the successful S_N2 displacement of the benzenesulfonate group by the bromide ion, we were hopeful that the Arbuzov reaction could be carried out smoothly to effect the synthesis of diethyl 3,3-dicarboethoxycyclobutanephosphonate **(105)**.

When carried out on a small scale (< 10 mg), treatment of diethyl 3-bromocyclobutanecarboxylate with excess triethyl phosphite (100 fold) (Scheme 2.4) appeared promising as a method of preparing diethyl 3,3-dicarboethoxycyclobutanephosphonate **(105)**. The reaction mixture was heated at 100 °C for 24 hours with an air condenser. Remaining triethylphosphite and any diethyl ethanephosphonate formed in the reaction were removed by distillation. ^1H Nmr analysis of the residue indicated that the distinctive quintet signal at 4.5 ppm, assigned to the proton attached to the same carbon as the bromine, had almost disappeared. The two individual multiplets, at 2.9 and 3.1 ppm, attributed to the methylene protons of the cyclobutane ring had broadened to one large multiplet (2.1-2.7 ppm) which now integrated to greater than four (~4.4). This indicated that the bromine had been displaced by something less electronegative, suggesting that the Arbuzov reaction had taken place. Mass spectrometry of the crude sample indicated that some of the desired product had formed (peak at 336 mass units corresponding to the molecular weight of diethyl 3,3-dicarboethoxycyclobutanephosphonate **(105)**), although some of bromocyclobutane **(100)** starting material was still present.

However, when the reaction was carried out on a multigram scale with a 5-10 fold excess of diethyl phosphite, under conditions in which the ethylbromide formed was removed from the reaction mixture by distillation, little of the desired product was formed. Removal of the unreacted triethyl phosphite yielded the starting alkylhalide and less than 5 % of the diethyl 3,3-dicarboethoxycyclobutanephosphonate **(105)**. Prolonged reaction times

and higher temperatures (> 125 h, 140 °C) did little to increase the yield. The low yield of product, despite the fact that the cyclobutane is able to undergo S_N2 reactions, is possibly due to the fact that the phosphite is a weaker nucleophile than the bromide ion used in the S_N2 substitution and the bromide ion is a poorer leaving group than the benzenesulfonate.



(100)

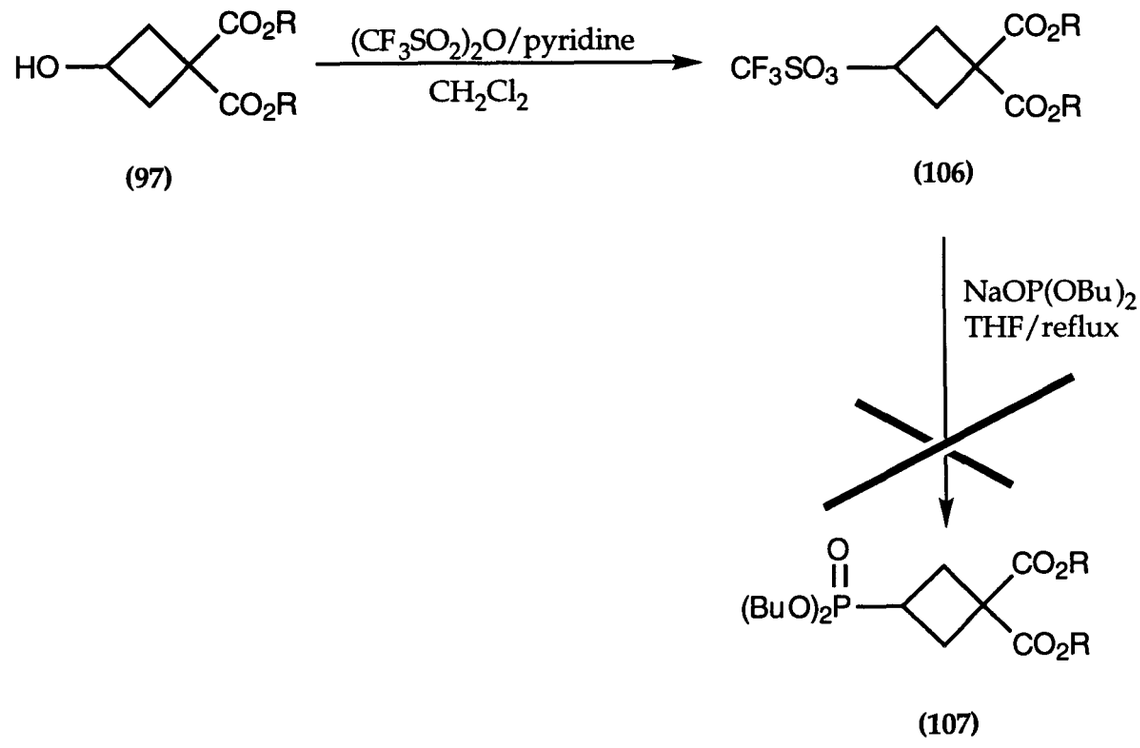
(105)
< 5 %

Scheme 2.4.

Reports in the literature indicate that a better procedure for the formation of the carbon-phosphorus bonds is a modified Arbuzov reaction, using the sodium salt of dibutyl phosphonate to displace trifluoromethanesulfonate as the leaving group.[86] The sodium salt is used so that the by-product is the salt, sodium trifluoromethanesulfonate, which will not compete as a substrate in the reaction. The butyl phosphite ester is used in preference to methyl or ethyl esters because the sodium dibutylphosphite is soluble, unlike the sodium salts of the lower esters, thus avoiding solubility problems. As trifluoromethanesulfonate is a better leaving group than a bromide ion, it was expected that this would facilitate the displacement reaction at the secondary carbon.

The alcohol was converted into diethyl 3-(trifluoromethanesulfonyloxy)cyclobutanedicarboxylate **(106)** in quantitative yield by treatment with trifluoromethanesulfonyl anhydride and triethylamine in dichloromethane at 0 °C (Scheme 2.5). After extractive work up using ice cold water, the triflate was used without further purification. Sodium dibutylphosphite was formed by the addition of sodium metal to

tributylphosphite in anhydrous THF. The triflate **(106)**, in a solution of THF, was added to the reaction mixture which was refluxed for two days. After work up and distillation, ^1H nmr analysis indicated that none of the desired dibutyl 3,3-dicarboethoxycyclobutanephosphonate **(107)** had formed. The quintet at 5.3 ppm due to the proton geminal to the triflate group was still clearly visible. Interestingly no evidence was seen of any elimination of the trifluoromethanesulfonic acid to form the cyclobutene. Elimination of secondary triflates under the reaction conditions described above is quite common. One possible explanation for the total absence of any elimination product is the inability of the cyclobutane ring to adopt a conformation such that the proton β to the triflate group is antiperiplanar to the triflate, preventing elimination from occurring *via* an E_2 mechanism.

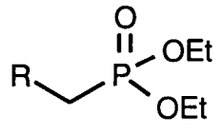


(97) **(106)** **(107)**

Scheme 2.5.

2.3. Synthesis of Cyclobutanes using Stabilised Carbanions other than Malonates

As the Arbuzov reaction was not a suitable method of producing the desired diethyl 3,3-dicarboethoxycyclobutanephosphonate on a preparative scale, it was necessary to investigate other routes to the target compounds. One method that appeared promising was to exploit the phosphonate functionality as an integral part of the ring synthesis, using compounds **(108-111)** (Figure 2.6) which are analogues of dialkyl malonates, where one of the carboxylic ester groups is replaced by a phosphonate ester and the other by a second electron withdrawing group which could be removed after cyclobutane had formation. As sulfur is easily removed from most compounds by reaction with Raney nickel, we decided, initially, to investigate reactions in which the second carboxylic ester group was replaced by a sulfur-containing functional group, the trimethylsilyl group also appeared as a promising alternative.



(108) R=SO_2R'
(109) R=SOR'
(110) R=SR'
(111) R=$SiMe_3$

Figure 2.6: Phosphonate Analogues of Dialkyl malonate

2.3.1. α-Phosphoryl Sulfoxides as Malonate Analogues

It has been reported that [(phenylsulfonyl)methylene]dilithium, generated from methyl phenyl sulfone **(112)** and two equivalents of *n*-butyllithium in THF, reacts readily with a series of bifunctional organic substrates, such as dihalides and haloepoxides, amongst others, to give carbocyclic compounds in good yields (Figure 2.7).[87] The geminal dianion of

methyl phenyl sulfone reacts with epichlorohydrin **(113)**, attacking first at the epoxide followed by cyclisation to give the 1-(phenylsulfonyl)-3-hydroxycyclobutane **(114)**. If the initial attack were to occur at the carbon-halide centre, then the resulting intermediate would cyclise to give the smaller cycloalkane.[88]

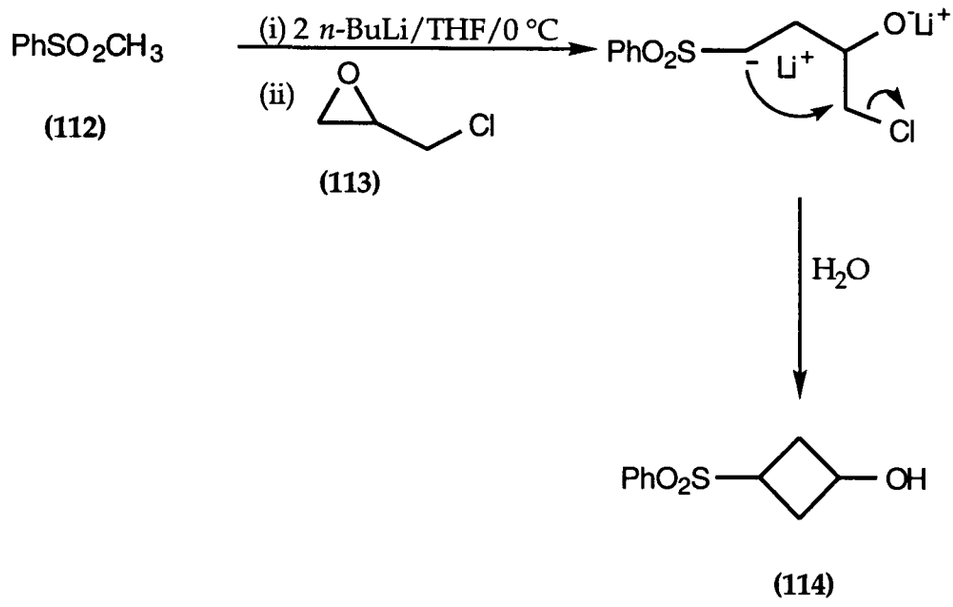
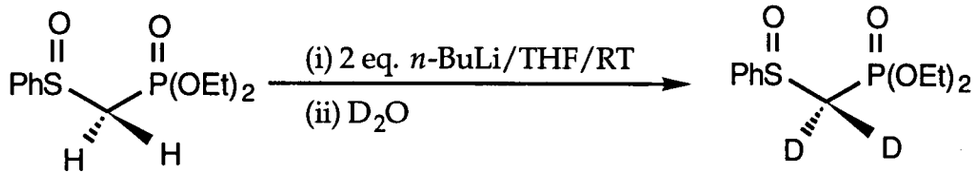


Figure 2.7: Reaction of [(Phenylsulfonyl)methylene]dilithium with Epichlorohydrin

As it can be difficult to cleanly remove the sulfone functionality from organic compounds using Raney nickel, we decided to study the ability of α-phosphoryl sulfoxides to form geminal dilithio salts, and the reaction of these salts with difunctional electrophilic compounds. Diethyl phosphorylmethyl phenyl sulfoxide **(115)** was prepared by oxidation of the commercially available diethyl phosphorylmethyl phenyl sulfide using sodium metaperiodate.[89] Although the monolithium salt of diethyl phosphorylmethyl phenyl sulfoxide is known to decompose at temperatures above -50 °C,[90] the dilithio salt did not form at temperatures below 0 °C. Generation of the geminal dilithio salt of diethyl phosphorylmethyl phenyl sulfoxide (Scheme 2.6) was achieved by treating a THF solution of the sulfoxide **(115)** with two equivalents of *n*-butyllithium at room temperature,

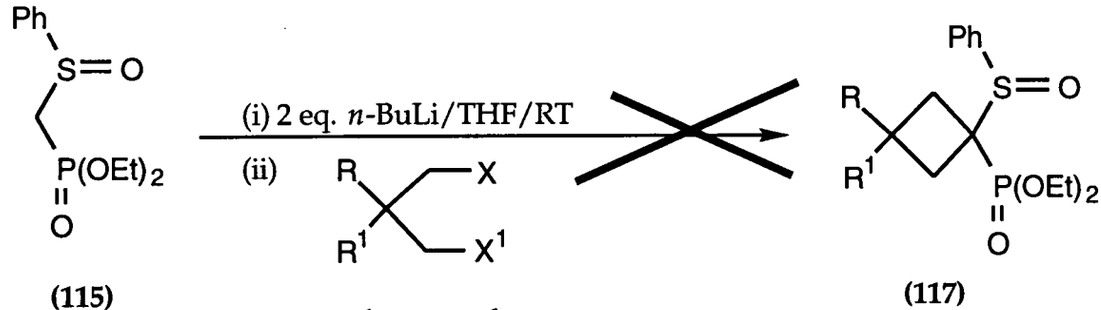
followed by cooling to -78 °C. Quenching this reaction mixture with deuterium oxide and analysis by ^1H nmr spectroscopy and mass spectrometry indicated that the geminal dianion had indeed formed. The ^1H nmr spectrum of the dideuterated **(115a)** compound showed almost no trace of the signals at 3.34 and 3.22 ppm due to the diastereotopic methylene protons. The mass spectrum showed a molecular ion of 278, two mass units greater than that of the undeuterated compound **(115)**.



(115) **(115a)**
> 95 %

Scheme 2.6.

Despite the formation of the geminal dianion, reaction with 1-chloro-2-benzyloxy-3-bromopropane **(91)** did not lead to cyclobutane formation, nor did reaction with 1,3-dibromo-2,2-dimethoxy-propane **(92)** or even the less hindered 1,3-dibromopropane **(89)** (Scheme 2.7). Various reaction conditions were investigated including different reaction temperatures (-78 to -40 °C) and different reaction times (one hour to 24 hours). However, in no case were any of the desired cyclobutane products **(117)** formed.



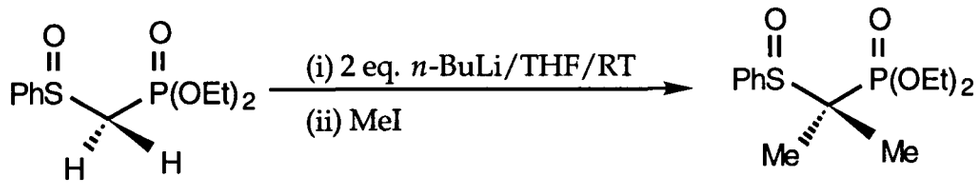
(115) **(117)**

(89) R=R^1=H, X=X^1=Br
(92) R=R^1=OMe, X=X^1=Br
(93) R=OCH$_2$Ph, R^1=H, X=Cl, X^1=Br
(116) R=R^1=H, X=X^1=OTf

Scheme 2.7.

Two factors may have been preventing the alkylation reaction occurring: firstly the bromine was not a sufficently good leaving group and secondly the size of the bromine may be hindering the electrophilic carbon to such an extent that the bulky carbanion was unable to get close enough to attack. To improve the ability of the leaving group and to some degree alleviate the bulk of the bromine functionality we decided to use 1,3-bis(trifluoromethanesulfonyloxy)propane **(116)** as a model compound (Scheme 2.7). Reaction of the geminal dilithio salt of diethyl phosphorylmethyl phenyl sulfoxide **(115)** with the bistriflate **(116)** returned only starting materials.

Unsuccessful reactions were also carried out in the presence of potassium *t*-butoxide, crown ether, TMEDA and HMPA. Reaction of the monolithium salt with methyliodide is known to give diethyl phosphoryl(1-methylmethyl) phenyl sulfoxide.[91] Likewise, we found that the reaction of the dilithio salt of diethyl phosphorylmethyl phenyl sulfoxide **(115)** (Scheme 2.8) with two equivalents of methyliodide gives diethyl phosphoryl(1,1-dimethylmethyl) phenyl sulfoxide **(118)**.

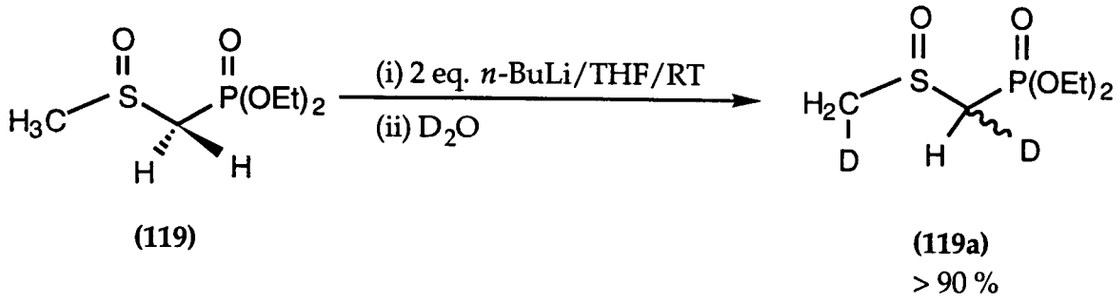


(115) **(118)**
> 95 %

Scheme 2.8.

Attempts to form the geminal dianion of diethyl phosphorylmethyl methyl sulfoxide **(119)** (Scheme 2.9), as a less hindered and slightly less stabilised alternative to the phenyl sulfoxide, were unsuccessful. Addition of two equivalents of *n*-butyllithium followed by a deuterium oxide quench indicated that only one of protons α to both the sulfoxide and the phosphonate

functionalities had been removed and that the second proton was removed from the methyl group to give the 1,3-dideuterated compound **(119a)**.



(119) **(119a)** > 90 %

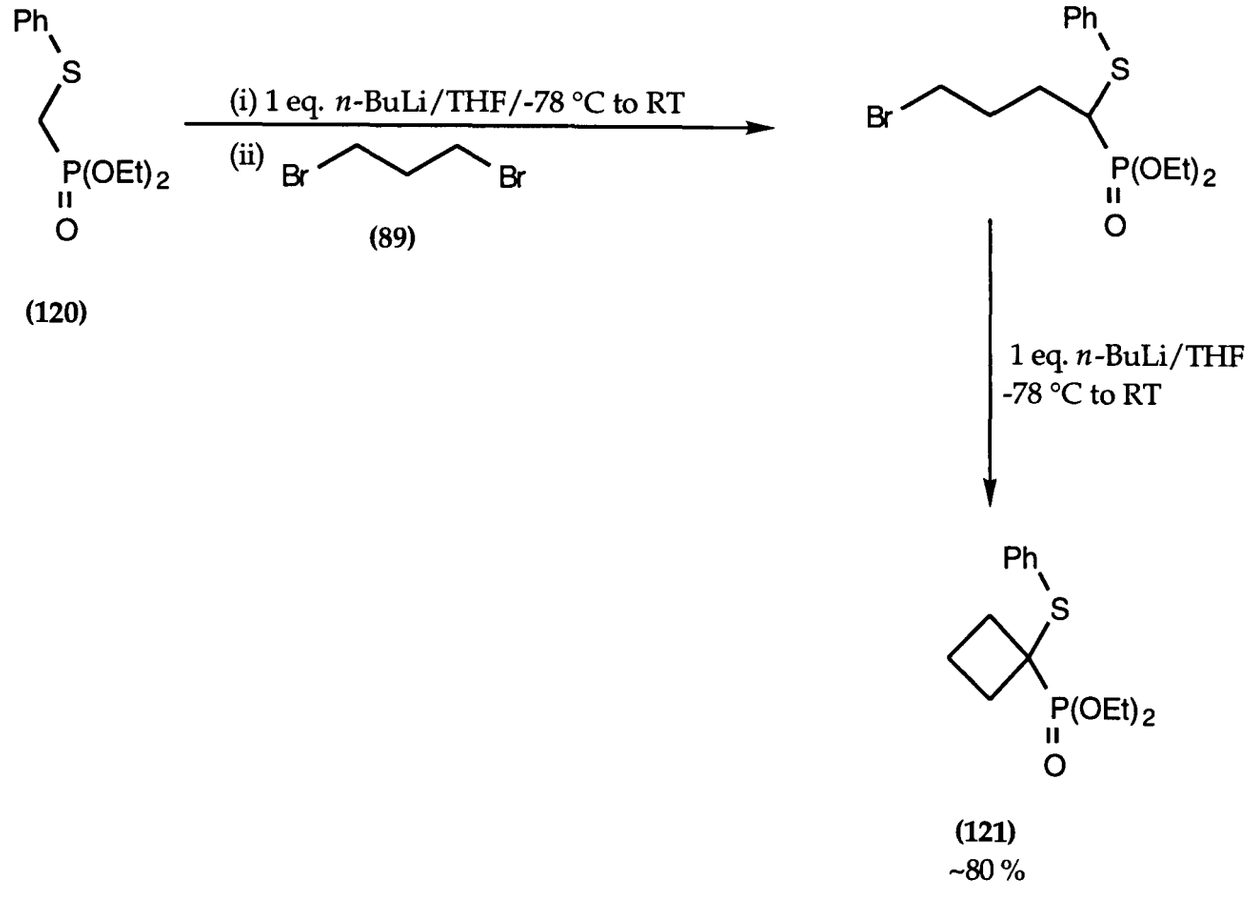
Scheme 2.9.

Since the lithium salt of diethyl phosphorylmethyl phenyl sulfoxide is known to react with carbonyl compounds in Wittig-Horner reactions[89] and we have shown that the dilithio salt can be methylated by reaction with methyliodide, the apparent inability of the dilithium salt to react with carbon-halide and carbon-triflate centres suggests that these centres may not electrophilic enough to undergo attack by this anion.

2.3.2. Diethyl α-Phosphorylmethyl Phenyl Sulfide as a Malonate Analogue

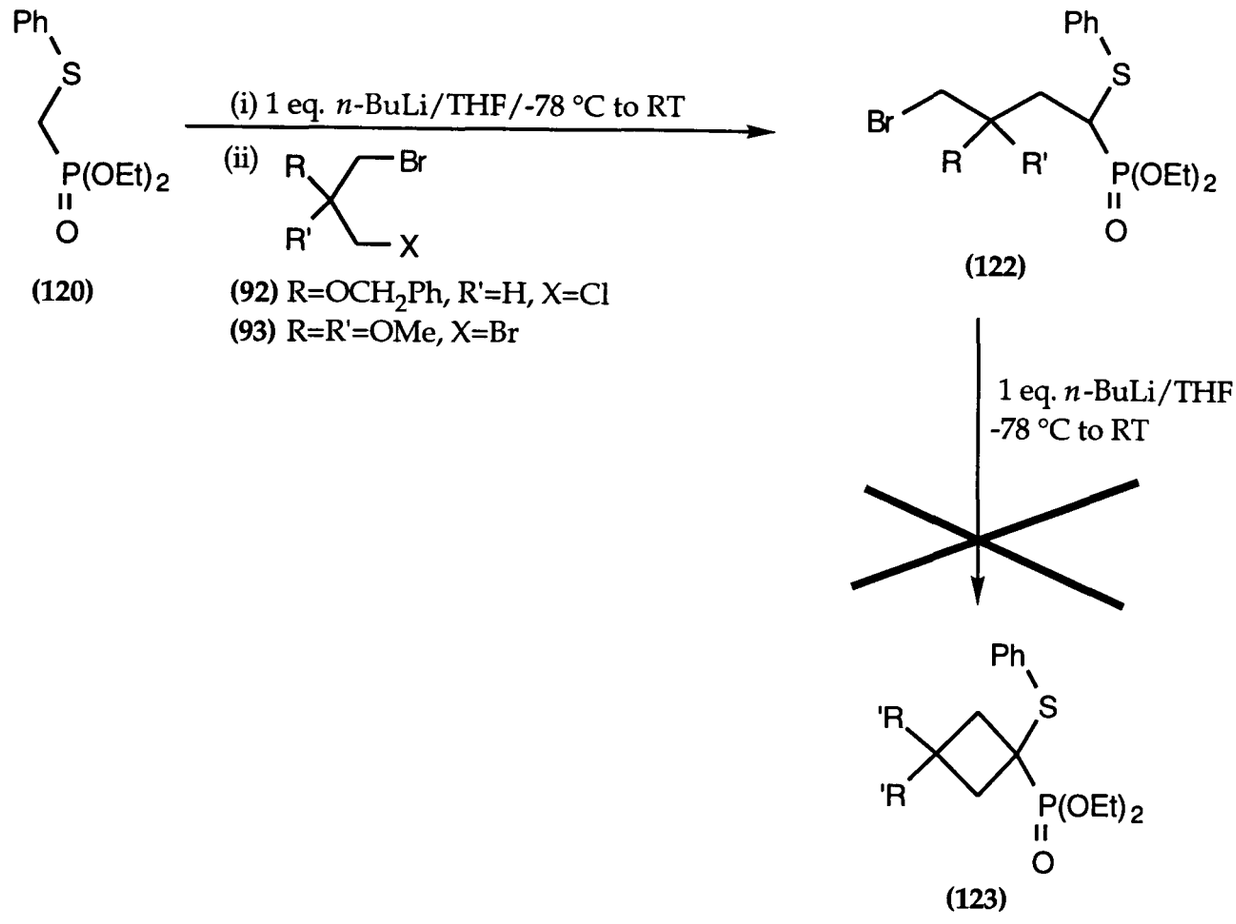
As the geminal dianions of α-phosphoryl sulfoxides were found to be unsuitable as nucleophiles for formation of carbon-carbon bonds by displacing a bromide or triflate, we decided to investigate α-phosphorylsulfides. The geminal dianion of diethyl phosphorylmethyl phenyl sulfide **(120)** is not formed by treatment of this compound with *n*-butyllithium, *s*-butyllithium or *t*-butyllithium at room temperature, 0 °C or -78 °C. However, we found that reaction of the monoanion of diethyl phosphorylmethyl phenyl sulfide (Scheme 2.10) with the model compound, 1,3-dibromopropane **(89)** in THF at -78 °C, for one hour, followed by reaction at room temperature for one hour and subsequent cooling to -78 °C before the addition of a second equivalent of

n-butyllithium resulted in high yields of diethyl 1-(phenylthio)cyclobutanephosphonate **(121)**.



Scheme 2.10.

Unfortunately, when the reaction was carried out using 1-chloro-2-benzyloxy-3-bromopropane **(91)** or 1,3-dibromo-2,2-dimethoxy-propane **(92)**, none of the desired cyclobutanes **(123)** are formed, only a small amount of the monoalkylated compound **(122)** and starting materials were isolated after work up (Scheme 2.11). Reaction with epichlorohydrin was similarly unsuccessful. The fact that a reaction occurs with 1,3-dibromopropane **(89)** but not with 2-substituted-1,3-dibromopropanes **(92 & 93)** indicates that the added bulk of the functional group at the 2-position may preventing the reactions from occurring.



Scheme 2.11.

2.3.3. Diethyl α-Trimethylsilylmethylphosphonate as a Malonate Analogue

Trimethylsilylmethyl phenyl sulfide **(124)** reacts with *n*-butyllithium and epibromohydrin **(125)** to form useful amounts of 1-(phenylthio)-3-(trimethylsilyloxy)cyclobutane **(126a)** and 1-(phenylthio)-3-hydroxy-cyclobutane **(126b)** (Figure 2.8). It is suggested that the cyclobutane products arise due to attack of the epoxide by the carbanion, opening of the epoxide, followed by a 1,4-migration of the trimethylsilyl group from the carbon to the oxygen generating a carbanion. This carbanion then undergoes intramolecular alkylation displacing the bromine, to form the cyclobutane product. The desilylated compound results from hydrolysis during work up of the reaction.[92] A similar reaction has been reported for α,α-bis(trimethylsilyl)methyllithium phenyl sulfide with epichlorohydrin.[93]

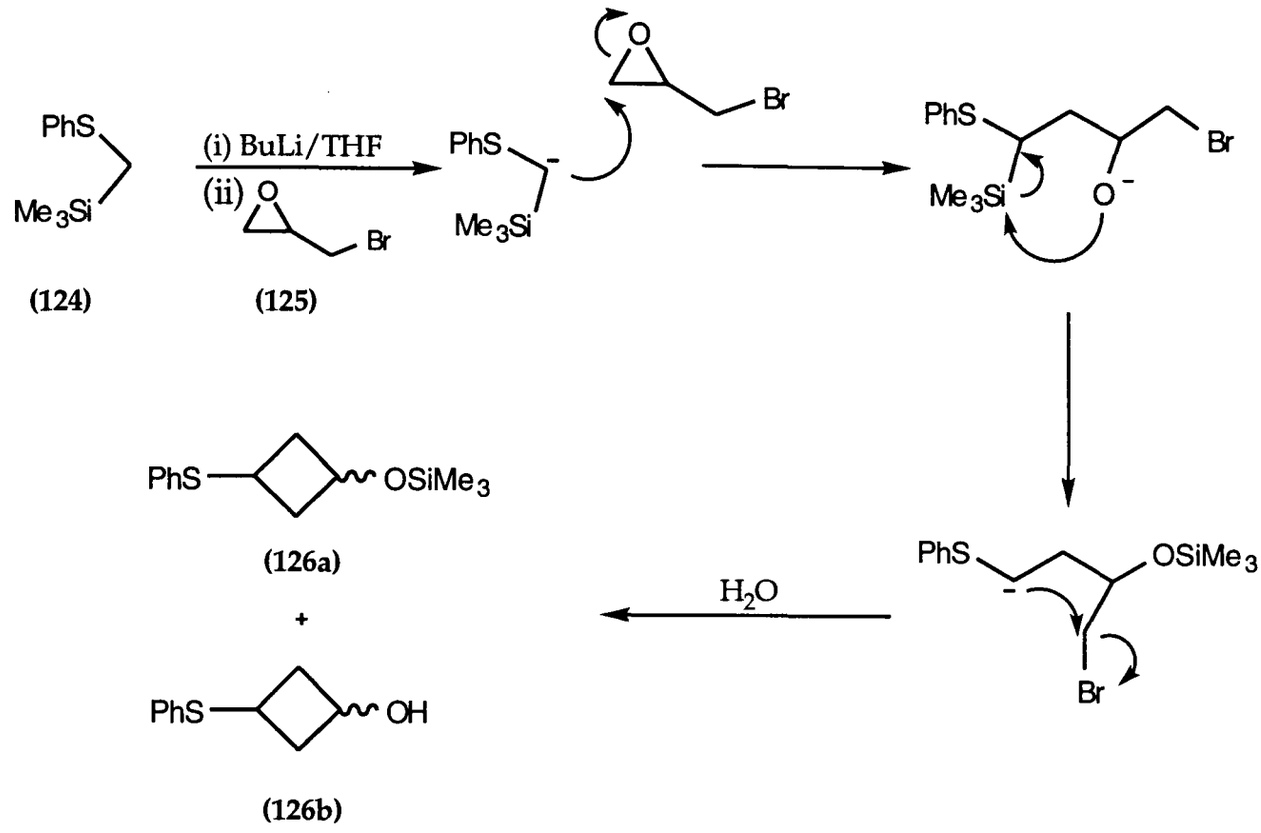
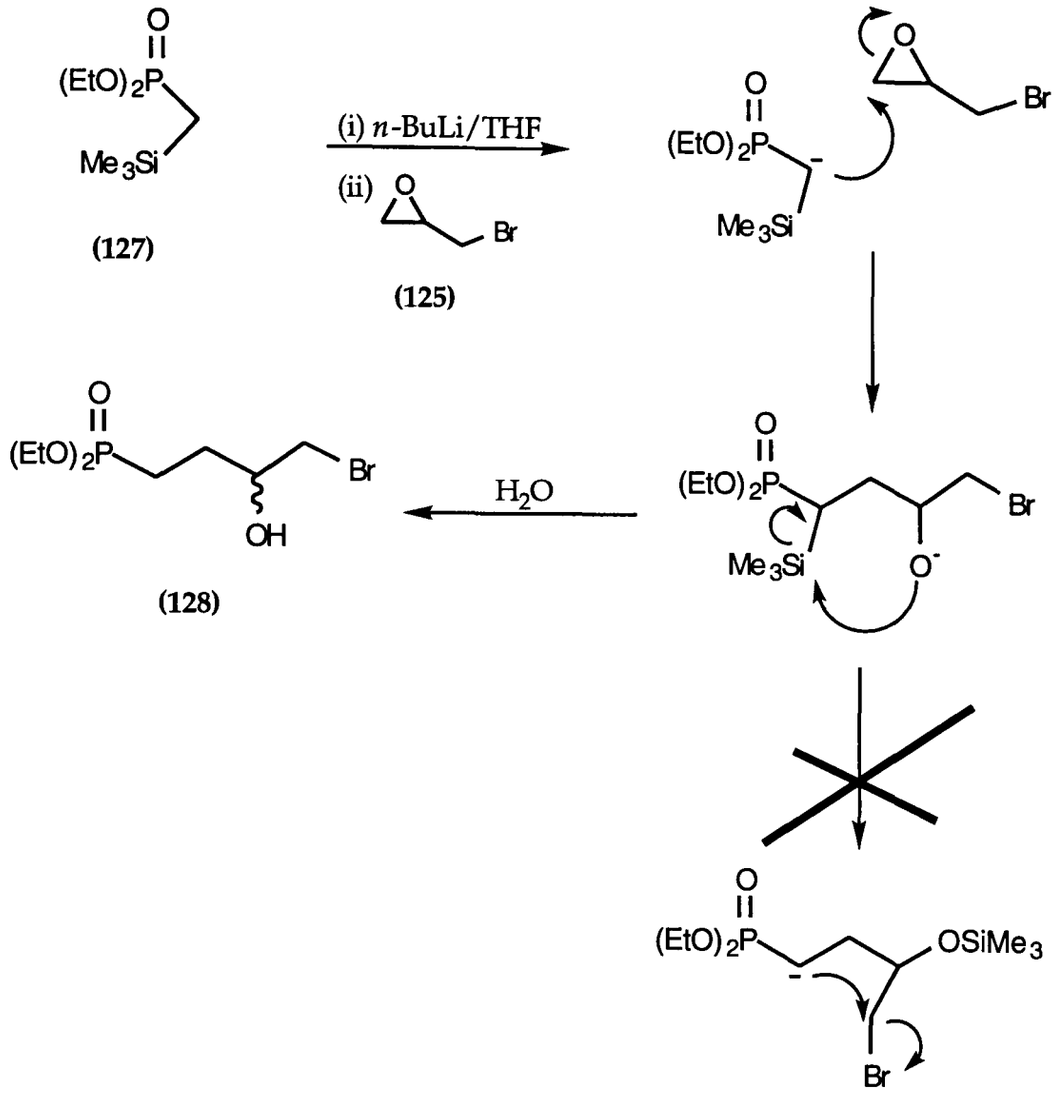


Figure 2.8: Synthesis of 1-Phenylthio-3-hydroxycyclobutane

As trimethylsilylmethyl phenyl sulfide **(124)** and bis(trimethylsilyl)methyl phenyl sulfide are both rather sterically hindered molecules, we hoped that even with the presence of a bulky phosphonate group our anion would be sufficiently reactive. Treatment of diethyl trimethylsilylmethylphosphonate **(127)** with *n*-butyllithium and epibromohydrin **(125)** at room temperature resulted only in the isolation of starting material (Scheme 2.12). Heating the reaction mixture to reflux resulted in the formation of diethyl 3-hydroxy-4-bromobutanephosphonate **(128)**. This suggested that carbanion attack of the epoxide and migration of the trimethylsilyl group occurred to give diethyl 3-(trimethylsilyloxy)-4-bromobutanephosphonate which did not cyclise, but was hydrolysed to the alcohol **(128)** on work up.

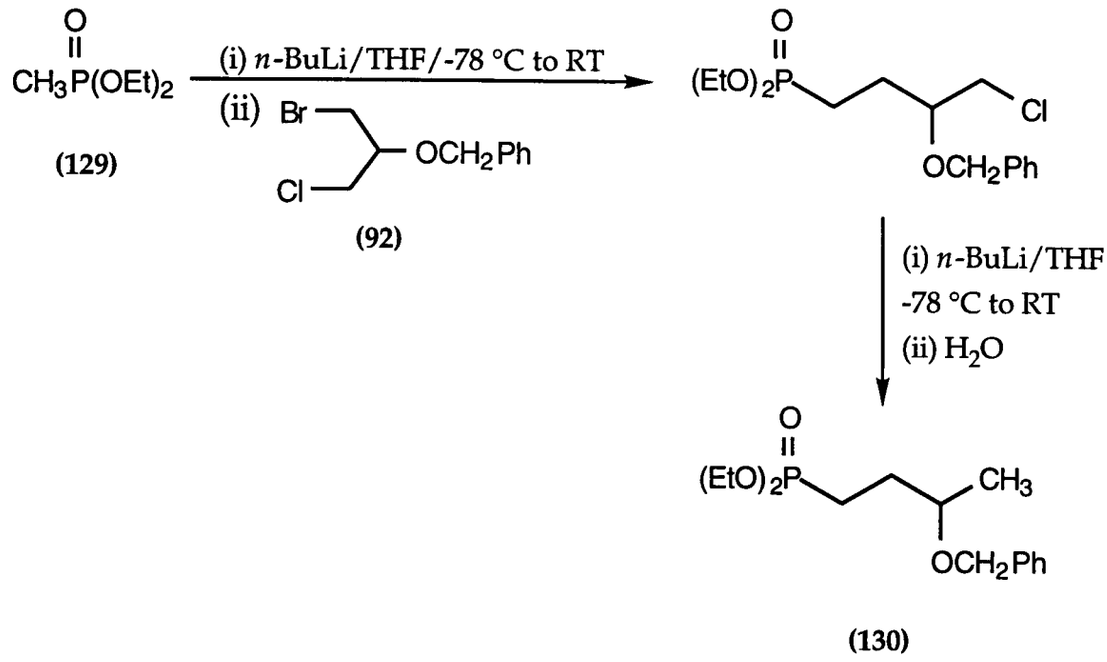


Scheme 2.12.

2.3.4. Synthesis of Diethyl 3-Oxocyclobutanephosphonate

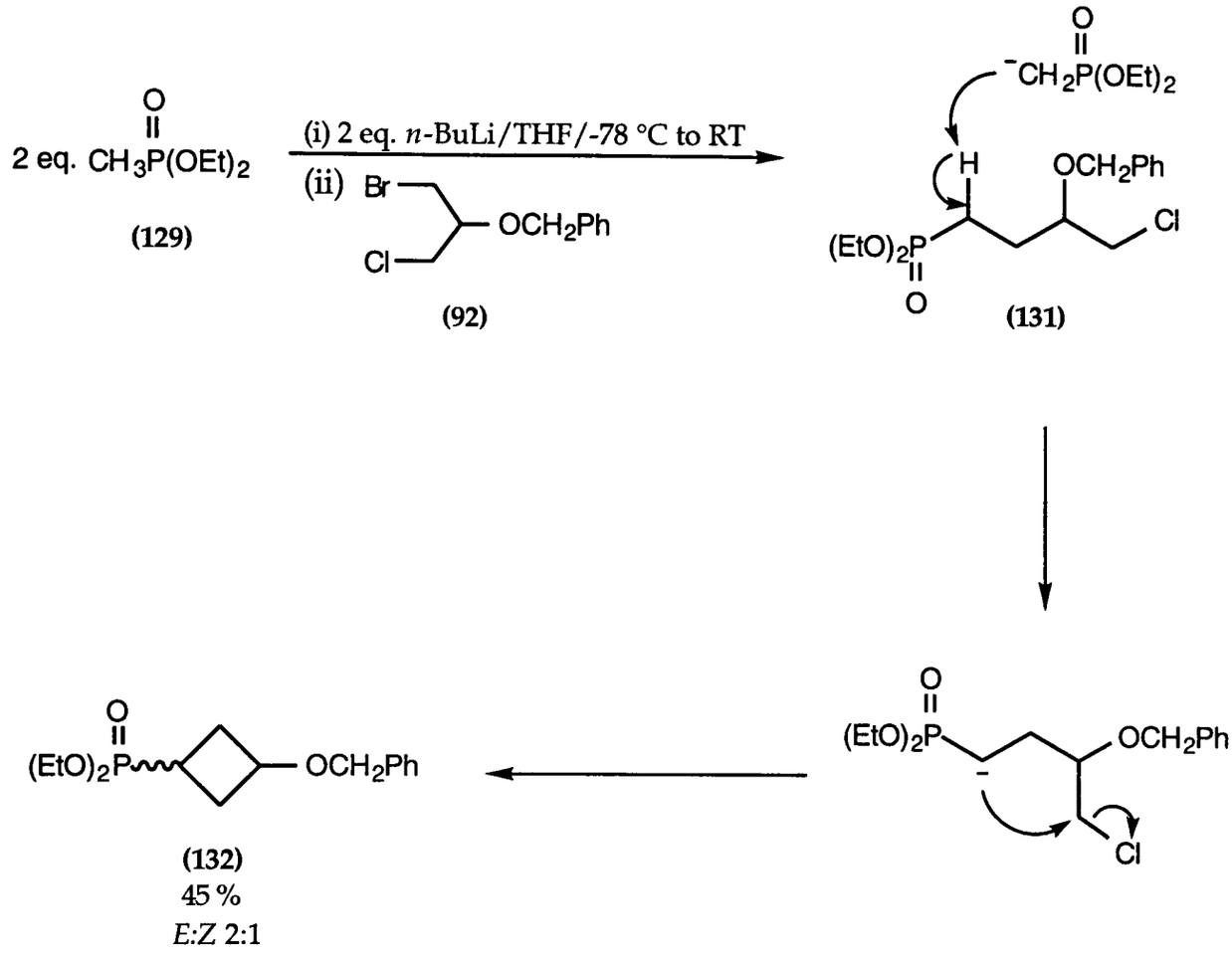
Since all the α-substituted phosphonate analogues of diethyl malonate that we investigated appeared to be too unreactive and/or too hindered to react with a 2-substituted-1,3-dihaloalkane, we decide to investigate reactions using diethyl methanephosphonate **(129)**. As was expected, the dianion of this compound could not be formed. Treatment of diethyl methanephosphonate **(129)** (Scheme 2.13) with *n*-butyllithium (or LDA), 1-chloro-2-benzyloxy-3-bromopropane **(91)** and a second equivalent of *n*-butyllithium (or LDA), sequentially, as with diethyl phosphorylmethyl phenyl sulfide, resulted only in the formation of diethyl 3-(benzyloxy)butanephosphonate **(130)**. Although the anion had formed and reacted with the alkylbromide, the addition of the

second equivalent of *n*-butyllithium appears to result in lithium-chloride exchange at a rate faster than abstraction of a proton α to the phosphonate group.



Scheme 2.13.

Reaction of two equivalents of diethyl methanephosphonate **(129)** with two equivalents of *n*-butyllithium and one equivalent 1-chloro-2-benzyloxy-3-bromopropane **(91)** results in the formation of diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)** in good yields for this type of cyclisation reaction (Scheme 2.14). We have suggested that the mechanism of the reaction is as follows: the addition of *n*-butyllithium results in the formation of the lithiophosphonate, which displaces the bromide to form a carbon-carbon bond. The second equivalent of the lithiophosphonate then acts as a base to abstract a proton α to the phosphonate group of the intermediate diethyl 3-(benzyloxy)-4-chlorobutanephosphonate **(131)**, which then cyclises, displacing the chloride to give the desired diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)**.



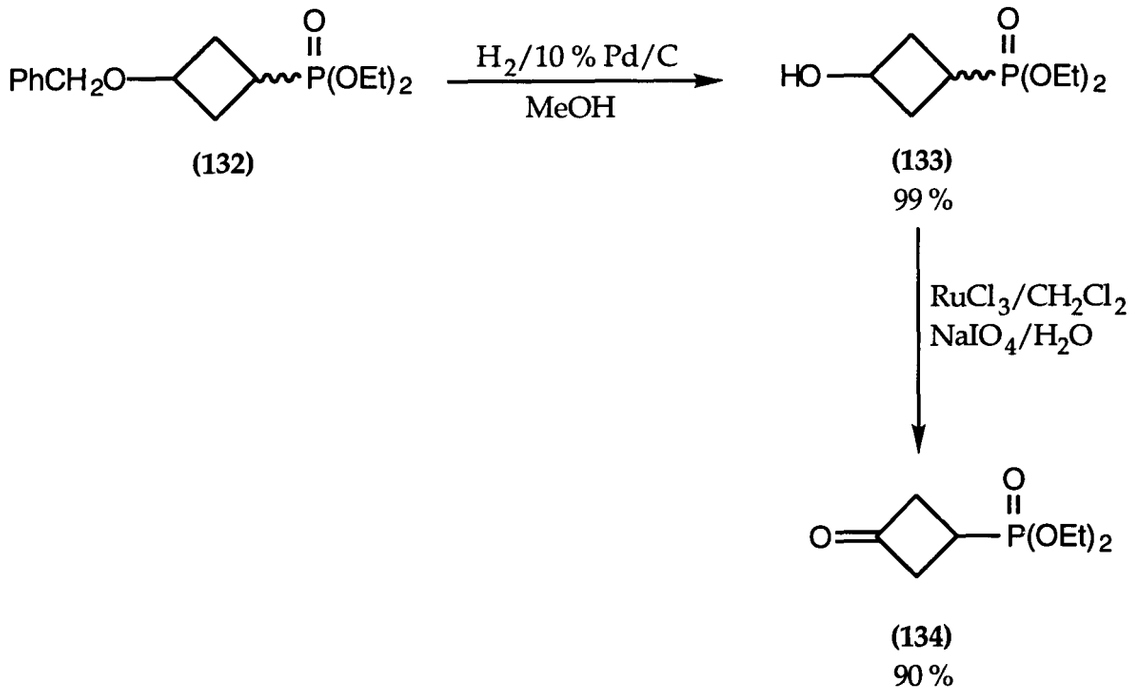
Scheme 2.14.

The cyclobutanephosphonate **(132)** is formed as a 2:1 mixture of the two diastereoisomers. As the lithium cation can only be chelated by the carbanion and the phosphonate, chelation will not play a significant stereochemical directing role in this reaction. The stereochemistry is directed mainly by the steric interaction of the bulky substituents, thus the major isomer is most likely to be the *E*-isomer with the phosphonate and the benzyloxy substituents on opposite sides of the ring.

This reaction is also successful if the di-*iso*-propyl phosphonate ester is used, although the yield is slightly lower. However, if dimethyl methanephosphonate is used, only the monoalkalated intermediate, dimethyl 3-(benzyloxy)-4-chlorobutanephosphonate, is obtained. This suggests that the second equivalent of dimethyl lithiomethylphosphonate does not act as a base to abstract the second proton. One possible explanation for this may be that

the smaller ester groups of dimethyl methanephosphonate allow greater aggregation of the dimethyl lithiomethylphosphonate, making it more stable than the diethyl lithiomethylphosphonate and thus not able to abstract the second proton from dimethyl 3-(benzyloxy)-4-chlorobutanephosphonate.

Diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)** was isolated as a crude residue after unreacted starting material and any remaining diethyl 3-(benzyloxy)-4-chlorobutanephosphonate **(131)** were removed by distillation under reduced pressure. The crude residue was then purified by Kugelrohr distillation to give pure diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)**. The benzyl protecting group was removed in quantitative yield by hydrogenation over palladium on carbon (Scheme 2.15). The alcohol **(133)** was oxidised without further purification to give diethyl 3-oxocyclobutanephosphonate in high yields **(134)**.



(132)

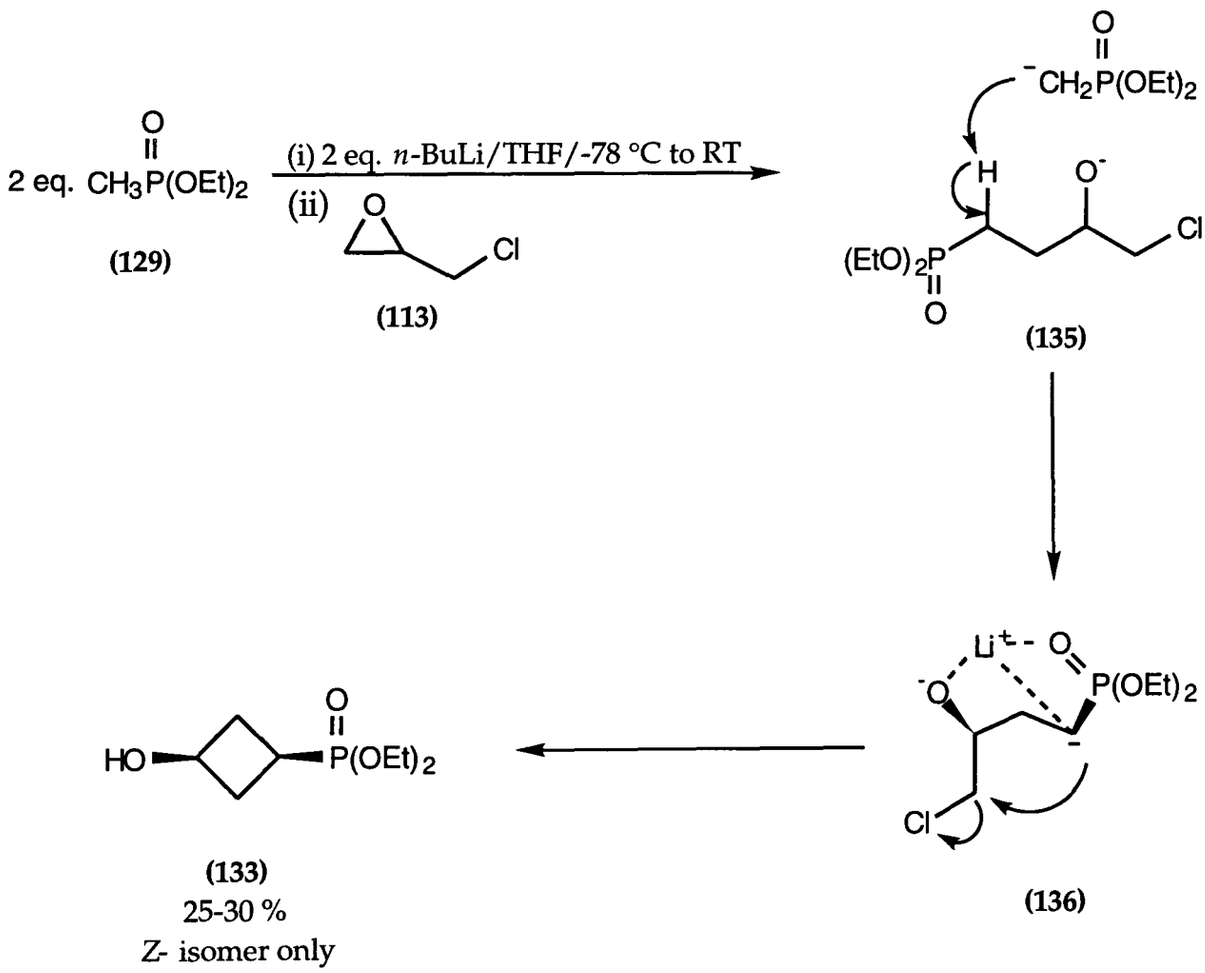
(133)
99 %

(134)
90 %

Scheme 2.15.

2.3.5. Synthesis of Diethyl 3-Hydroxycyclobutanephosphonate from Epichlorohydrin

Due to the success of the reaction between the anion of diethyl methanephosphonate **(129)** and 1-chloro-2-benzyloxy-3-bromopropane **(91)** we decided to investigate the reaction between the anion of diethyl methanephosphonate and epichlorohydrin **(113)** as a simpler procedure for the preparation of diethyl 3-hydroxycyclobutanephosphonate **(133)** (Scheme 2.16). Again, two equivalents of diethyl methanephosphonate **(129)** and *n*-butyllithium were required to react with one equivalent of epichlorohydrin **(113)**. Diethyl 3-hydroxycyclobutanephosphonate **(133)** was produced in approximately 25-30 % yield.



Scheme 2.16.

Unfortunately, separation of the diethyl 3-hydroxy-cyclobutanephosphonate **(133)** from monosubstituted diethyl 3-hydroxy-4-chlorobutanephosphonate **(135)** by distillation proved to be problematic. These two compounds could not be separated by Kugelrohr distillation. Distillation through a vigreux column gave some separation. However, to obtain pure diethyl 3-hydroxycyclobutanephosphonate **(133)** several distillations were required. Thus, we used the 1-chloro-2-benzyloxy-3-bromopropane method for the synthesis of diethyl 3-hydroxycyclobutanephosphonate **(133)** in this project.

In contrast to the 1-chloro-2-benzyloxy-3-bromopropane method, the reaction with epichlorhydrin produced only one diastereoisomer. The signals in the ^{13}C nmr spectrum of this compound corresponded to the signals that we had assigned to the *Z*-isomer of diethyl 3-hydroxycyclobutanephosphonate produced by hydrogenation of *E* / *Z*-diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)**. This can be explained by chelation of the lithium in the intermediate **(136)** by both the alkoxide and the phosphonate, holding these two groups *cis* to each other. A similar situation has been described in the reaction of 4-phenyl-4-(phenylsulfonyl)-1,2-epoxybutane **(137)** with two equivalents of methylmagnesium bromide (Figure 2.9). This reaction produces only one isomer of phenyl 3-phenyl-1-hydroxycyclobutanesulfonate **(138)**, which has been unambiguously shown to be the *Z*-isomer by X-ray structure determination. In this case the *cis* relationship is proposed to occur due to chelation of the magnesium by the alkoxide ion and the sulfone, in a system that is analogous to the alkoxide-lithium-phosphonate system described above.[88]

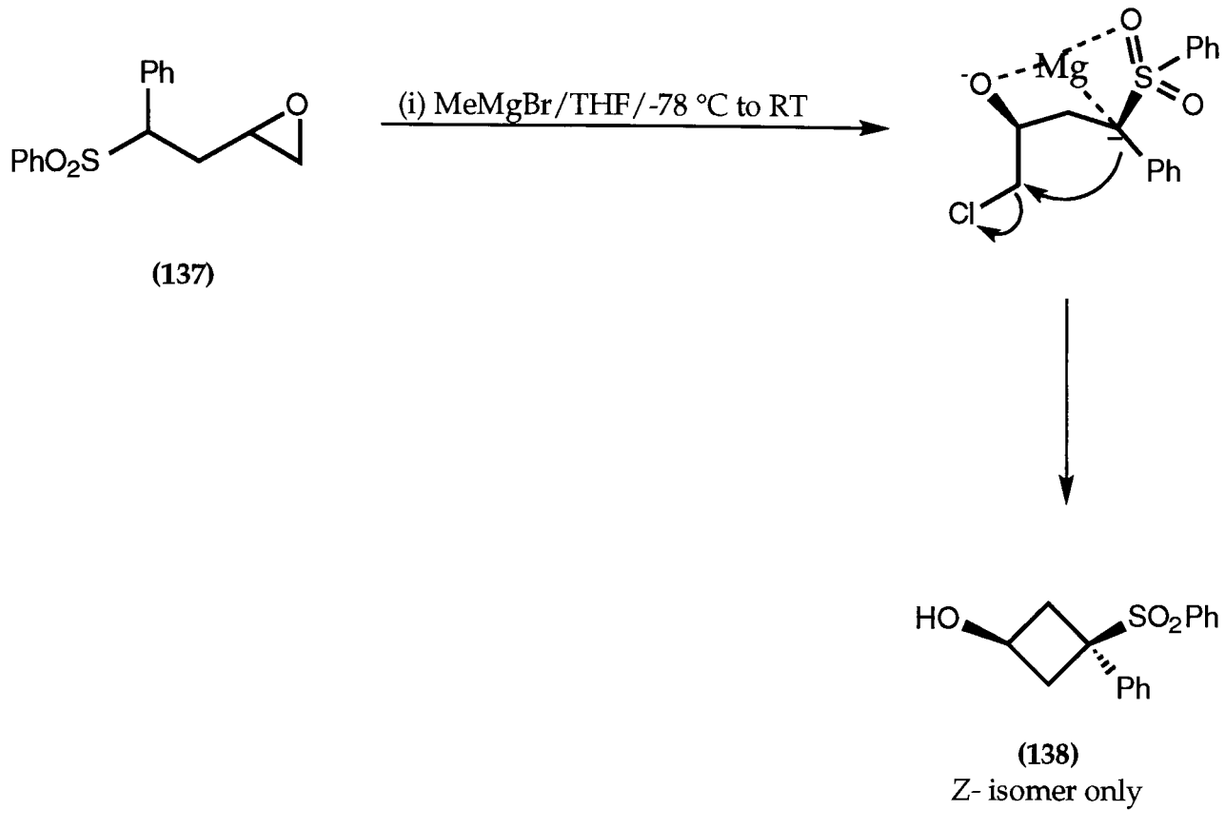


Figure 2.9: Synthesis of *Z*-3-Phenyl-3-phenylsulfonylcyclobutanol

2.4. Conclusion

The synthesis of the previously unknown compound, diethyl 3-oxocyclobutanephosphonate **(134)** has been described. This compound is a versatile synthetic intermediate which can be further functionalised to provide a range of 3-substituted-cyclobutanephosphonic acids and related compounds.

Chapter 3

Synthesis of Aminoacid Cyclobutanephosphonic Acids

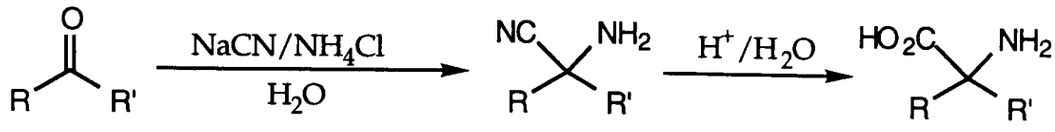
3.1. Introduction

Ketones are versatile synthetic intermediates that can undergo conversion into a number of other functional groups, including amines (*via* oximes), amino acids, cyanohydrins, α-hydroxy acids, epoxides and olefins. Ketones can also be transformed to their homologous aldehydes by Wittig-Horner type reactions.

Having prepared the key intermediate diethyl 3-oxocyclobutanephosphonate **(134)**, the synthesis of a number of interesting compounds became possible *via* elaboration of the 3-oxo functionality. In particular, the synthesis of 3-amino-3-carboxycyclobutanephosphonic acid and related phosphonic acids could now be attempted. There are two well known methods for the conversion of a carbonyl group into an α-amino acid functionality. The first and perhaps the most widely used is the Strecker reaction and the second is the Bucherer-Bergs reaction.[94, 95]

3.1.1. The Strecker Reaction

The original Strecker synthesis (Figure 3.1) involved the reaction of an aldehyde or ketone **(139)** with sodium or potassium cyanide and ammonium chloride in an aqueous environment to give an α-aminonitrile **(140)** *via* an iminium ion intermediate. The α-aminonitrile is then hydrolysed to the amino acid **(141)**. The main problem with this reaction is its sensitivity to the substituents on the ketone. In a number of cases, competing condensation reactions, long reaction times and low yields are observed.



(139) (140) (141)

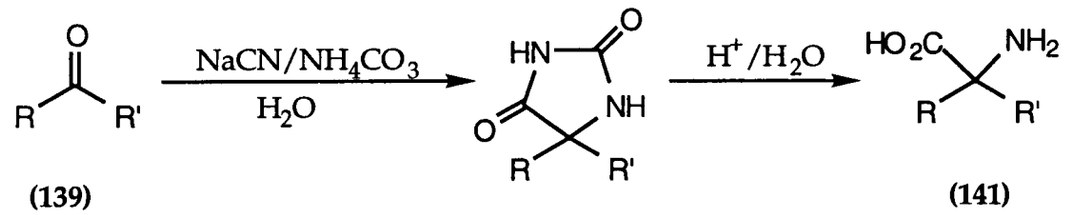
R=alkyl, aryl
R'=alkyl, aryl, H

Figure 3.1: The Strecker Amino Acid Synthesis

Several modifications of the Strecker reaction have now been reported. These include: the use of ultrasonic irradiation to catalyse the reaction in a non-aqueous environment;[96, 97] the use of substituted amines in place of ammonium chloride;[98] and the use of diethyl phosphorocyanidate in place of inorganic cyanide.[99] All these modifications are reported to give higher yields than the original Strecker reaction, but again there are limits to the range of ketone and aldehyde substrates.

3.1.2. The Bucherer-Bergs Reaction

The Bucherer-Bergs amino acid synthesis (Figure 3.2) involves the reaction of a ketone or aldehyde **(139)** with sodium cyanide and ammonium carbonate to give a hydantoin intermediate **(142)**. The hydantoin is then hydrolysed to the amino acid **(141)**. The Bucherer-Bergs reaction is reported to give higher yields and, in some cases, different isomeric mixtures of products to the Strecker reaction.[95]



(139) (142) (141)

R=alkyl, aryl
R'=alkyl, aryl, H

Figure 3.2: The Bucherer-Bergs Amino Acid Synthesis

Our initial attempts at the synthesis of *E*- and *Z*-3-amino-3-carboxy-cyclobutanephosphonic acids **(78)** concentrated on the Strecker reaction of diethyl 3-oxocyclobutanephosphonate **(134)** since we felt that this would give rise to a more equal mixture of the diastereoisomers. We also thought that the easiest way to separate a mixture of the diastereoisomers would be *via* a derivative of the amino nitrile.

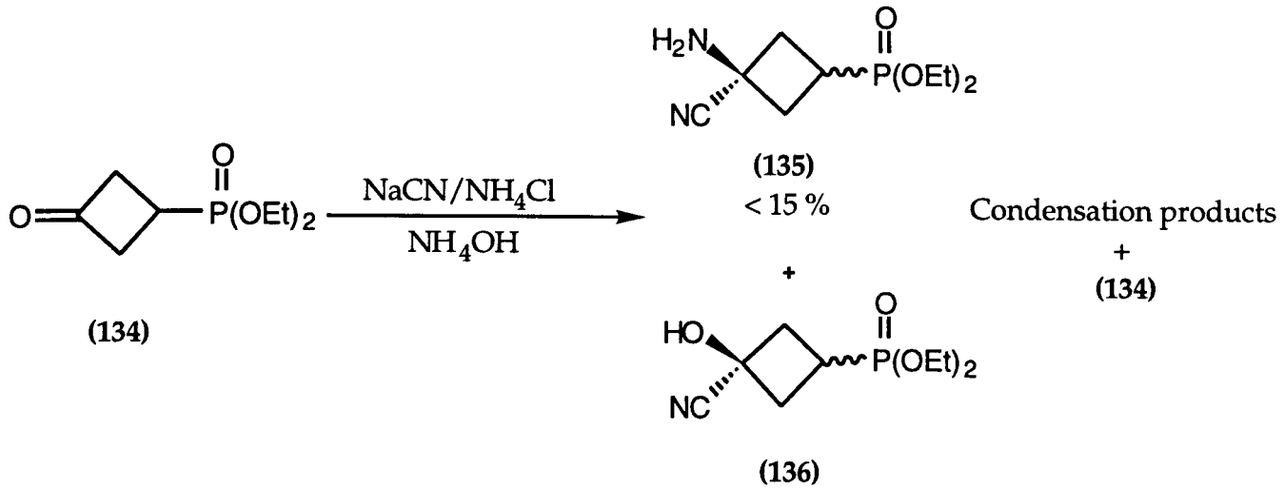
3.2. Synthesis of Diethyl 3-Amino-3-cyanocyclobutane-phosphonate

3.2.1. Reaction of Diethyl 3-Oxocyclobutanephosphonate Under Standard Strecker Conditions

The standard Strecker reaction conditions have been reported to be an acceptable method of converting a number of cyclobutyl, cyclopentyl and cyclohexyl compounds to the corresponding amino nitriles. Diethyl 3-oxocyclopentanephosphonate and diethyl 3-oxocyclohexanephosphonate were transformed to amino nitriles in 89 % and 88 % yields respectively.[77] Ethyl 3-oxocyclobutanecarboxylate, the carboxylic analogue of diethyl 3-oxocyclobutanephosphonate, was converted directly to 1-amino-cyclobutane-1,3-dicarboxylic acid in 48 % yield without isolation of the intermediate amino nitrile.[44] As these compounds are all similar to diethyl 3-oxocyclobutanephosphonate **(134)**, we attempted the synthesis of diethyl 3-amino-3-cyanocyclobutane phosphonate under the standard Strecker reaction conditions.

Reaction of diethyl 3-oxocyclobutanephosphonate **(134)** in concentrated ammonium hydroxide solution with sodium cyanide and ammonium chloride (Scheme 3.1), for 24 hours in the dark at room temperature, resulted in the formation of a number of products as shown by tlc. Work-up of the reaction, followed by analysis of the ^{1}H and ^{13}C nmr

spectra of the crude reaction mixture, suggested that although some of the desired aminonitrile **(135)** (< 15 %) had formed, large amounts of condensation products, some cyanohydrin **(136)** and some starting ketone were also present.

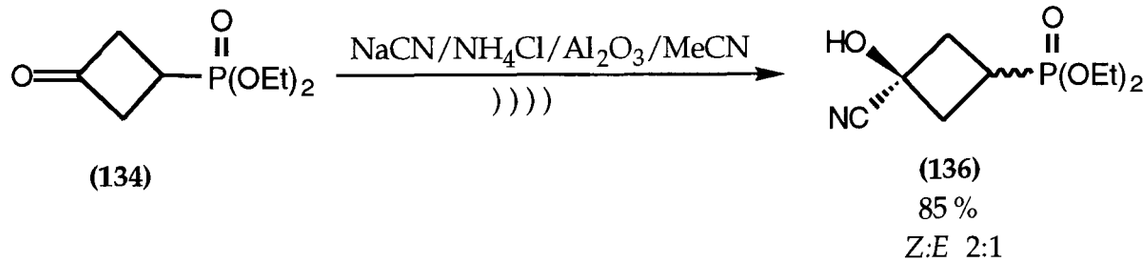


Scheme 3.1.

3.2.2. Synthesis of Diethyl 3-Cyano-3-hydroxycyclobutanephosphonate

As the standard Strecker reaction conditions were obviously unsuitable for a high yielding preparation of diethyl 3-amino-3-cyanocyclobutanephosphonate **(135)**, our attention turned to reports in the literature of high yielding modifications of the Strecker synthesis using ultrasonic irradiation. A number of 4-piperidone derivatives that could not be converted to α-aminonitriles in even moderate yields under normal conditions were converted quantitatively to amino nitriles by reaction with potassium cyanide and an amine in acetic acid under ultrasonic irradiation.[96] A procedure in which involves the heterogeneous reaction of a ketone with potassium cyanide, ammonium chloride and alumina in acetonitrile under ultrasonic irradiation has been reported to give high yields of amino nitriles, while suppressing the formation of cyanohydrins and condensation products.[97] This method has been used successfully in the synthesis of a number of 1-amino-3-cyanocyclopropanealkylphosphonates.[79]

Reaction of diethyl 3-oxocyclobutanephosphonate **(134)** with sodium cyanide, ammonium chloride and alumina in acetonitrile under ultrasonic irradiation (Scheme 3.2) for 12 hours resulted in a much cleaner reaction as indicated by tlc analysis. Further investigation of the crude product by ^{1}H and ^{13}C nmr indicated that only one compound, as a mixture of two isomers, (2:1 ratio), had been formed with less than 10 % of the starting material remaining. Infrared spectroscopy indicated that these compounds were not the aminonitriles **(135)** but the cyanohydrins **(136)**. The infrared spectrum showed a weak absorbance at 2221 cm^{-1} corresponding to the nitrile functionality and a strong broad absorbance at 3382 cm^{-1} corresponding to a hydroxyl group, rather than doublet in the region 3300 to 3400 cm^{-1} that would indicate the presence of an amino group. This was confirmed by elemental analysis of the phenylacetyl derivative **(138)**.

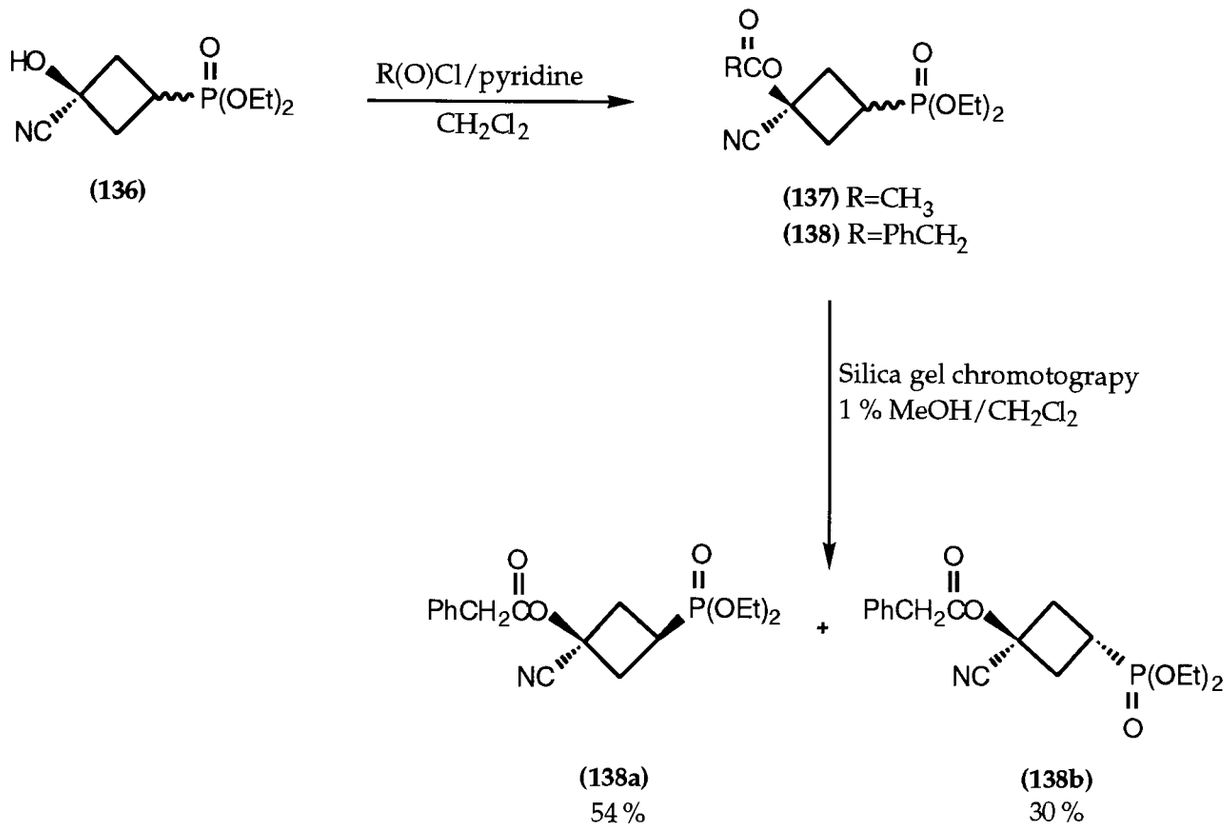


(134)

(136)
85 %
Z:*E* 2:1

Scheme 3.2.

As the cyanohydrin **(136)** is similar to the α-aminonitrile **(135)** we decided to use this compound as a model compound for studies on the separation and identification of the isomers. Separation of the *Z*- and *E*-cyclopentaneaminonitriles was achieved by chromatography of the *N*-acetyl derivatives on silica gel. A sample of the cyanohydrin **(136)** was converted to the *O*-acetyl derivative **(137)** (Scheme 3.3). Analysis by tlc using a variety of solvent systems gave only poor separation. However, conversion of the cyanohydrin to the phenylacetyl derivative **(138)** facilitated rapid separation of the isomers by silica gel chromatography.



Scheme 3.3.

3.2.2.1 Assignment of Configurations of Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutanephosphonate

Separation of the isomers allowed assignment of the configurations using ^{13}C nmr spectroscopy and X-ray crystallography. The major isomer from the crude reaction mixture was identified as the *Z*-isomer **(138a)** and the minor component as the *E*-isomer **(138b)**. Comparison of the ^{13}C nmr spectra of the two isomers showed a singlet for the peak at 117.93 ppm (Figure 3.3) for the isomer that eluted from the column first **(138a)**, and a doublet (J=3.2 Hz) at 117.12 ppm (Figure 3.4) for the compound that eluted second **(138b)**. These peaks correspond to the signal from the nitrile carbon indicating the compound that eluted from the column first is the *Z*-isomer **(138a)** and the second compound is the *E*-isomer **(138b)**. In the *E*-isomer the configuration of NC-C3-C2-C1-P is such that it forms a "w"-shape (Figure 3.5) and thus the

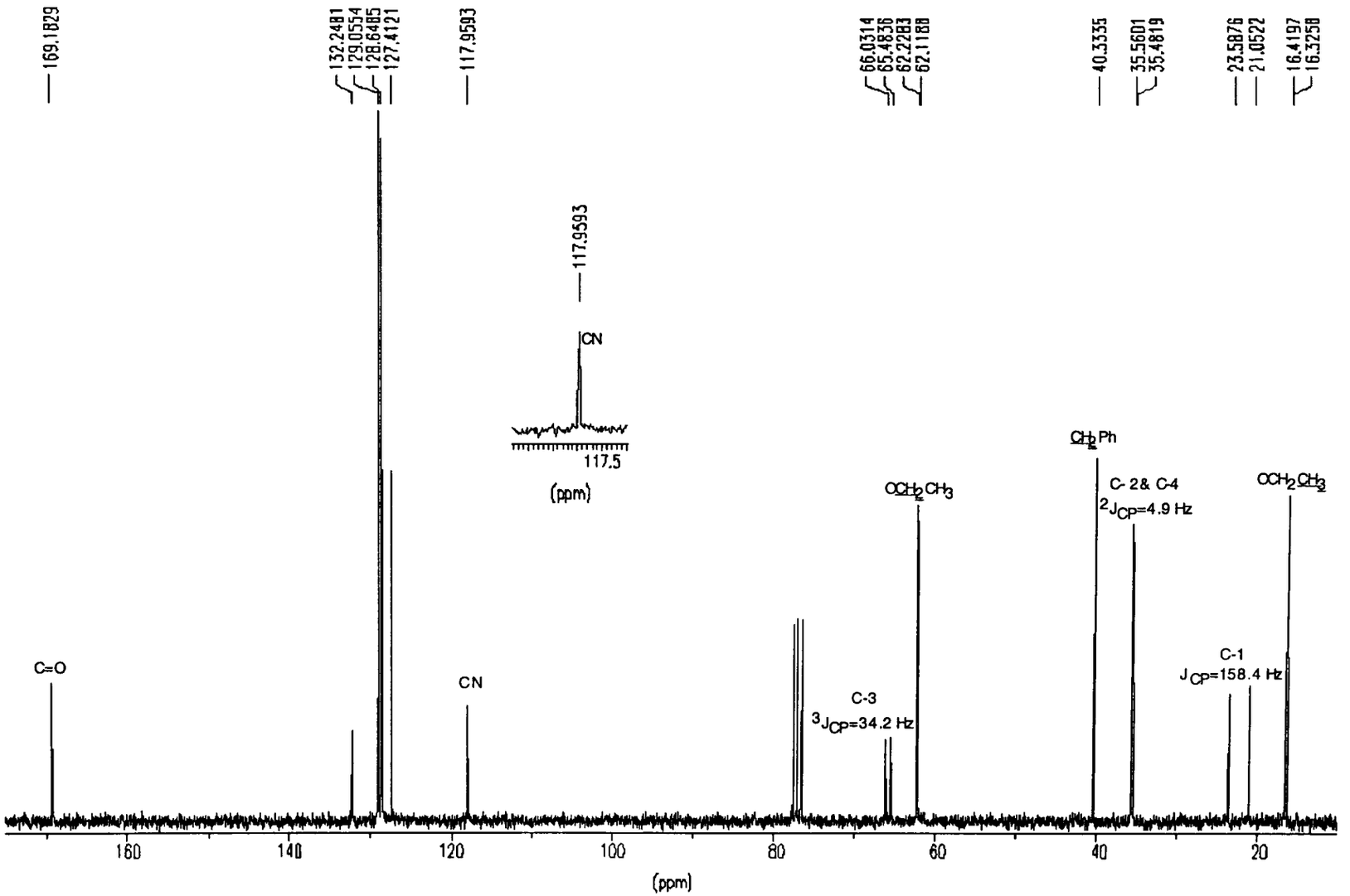


Figure 3.3: ^{13}C Nmr Spectrum of *Z*-Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutanephosphonate

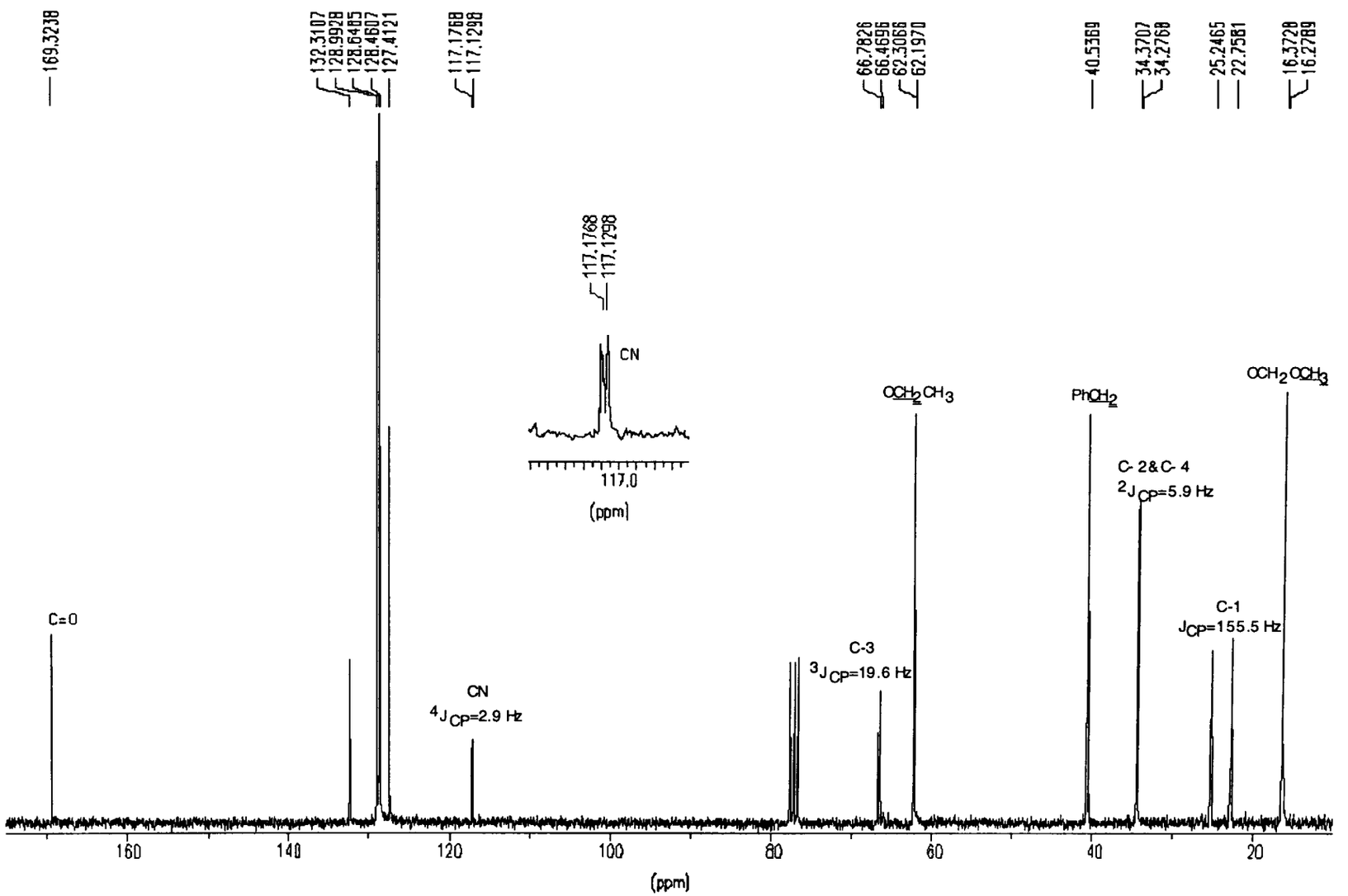
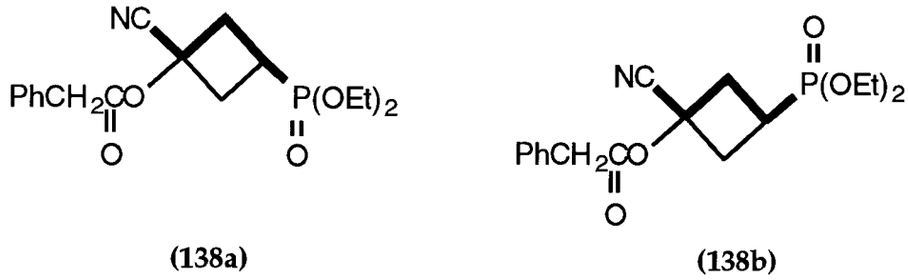


Figure 3.4: ^{13}C Nmr Spectrum of *E*-Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutanephosphonate

coupling between the phosphorus and the nitrile carbon is large enough to be seen (Figure 3.4), however in the *Z*-isomer **(139a)**, in which the phosphorus and the nitrile are on opposite faces of the cyclobutane ring, the configuration is such that no coupling will be observed (Figure 3.3).



(138a) **(138b)**

Figure 3.5: Configuration of *Z*- and *E*-Diethyl 3-(Phenylacetylamino)-3-cyano-cyclobutanephosphonate

There is also a considerable difference between the coupling constant of C3-P for each of the isomers. The *Z*-isomer has a value of $^{3}J_{CP}$=34.2 Hz which is significantly larger than the value for the *E*-isomer of $^{3}J_{CP}$=19.6 Hz. This suggests a difference in the ring conformation between the two isomers. The isomer identified as the *Z*-isomer was isolated as a white powder and crystallised slowly from a mixture of pentane, ether and toluene to give colourless crystals which were suitable for X-ray diffraction. This allowed the X-ray crystal structure of isomer 1 to be determined, thus confirming it as the *Z*-isomer (Figure 3.6). Bond lengths and angles associated with the cyclobutane ring **(138a)** are significantly strained, as is typical of four-membered rings. The dihedral angle C1-C2-C3-C4 is -14.7° illustrating the typical ring puckering of a cyclobutane.

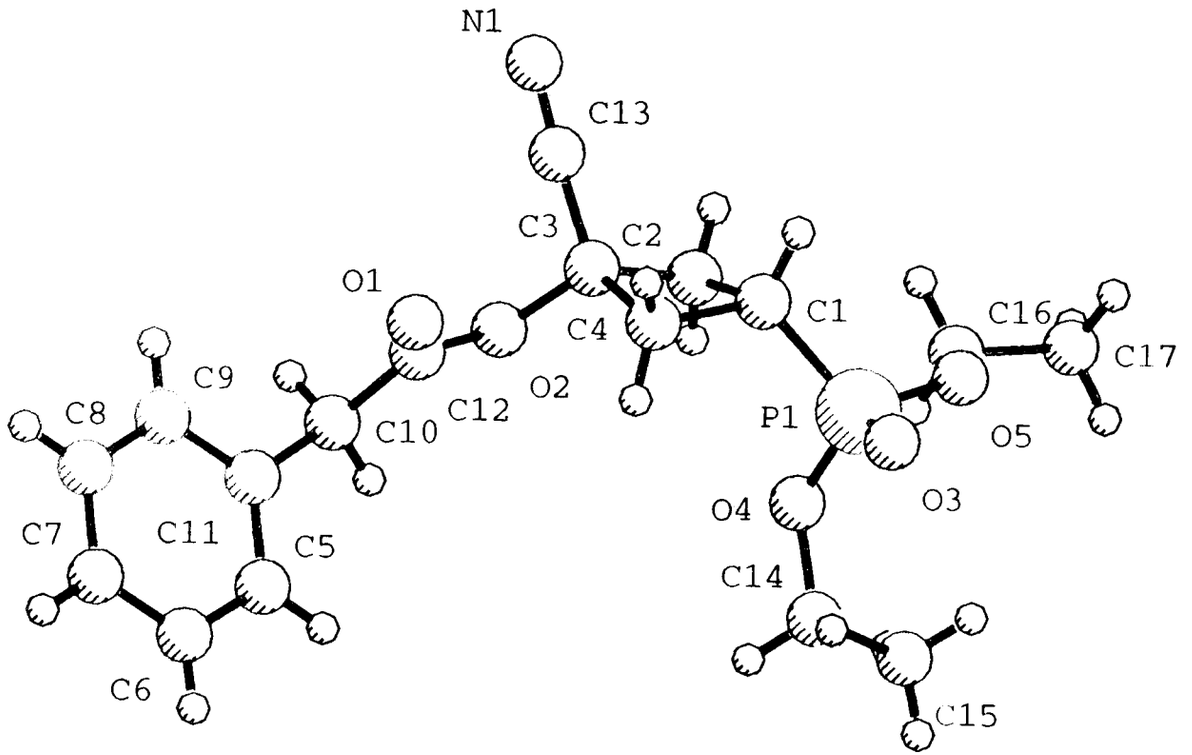
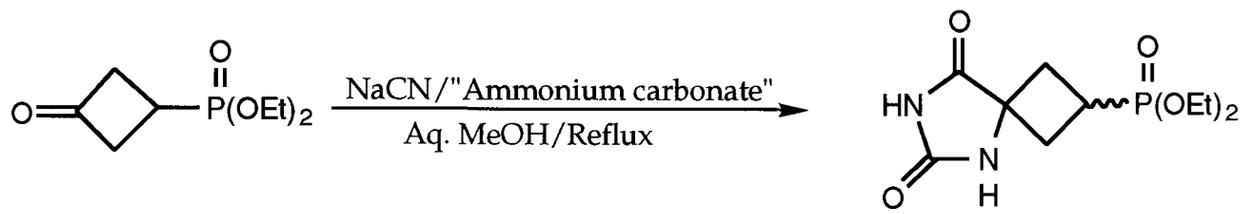


Figure 3.6: Ortep plot of *Z*-Diethyl 3-(Phenylacetoxy)-3-cyano-cyclobutanephosphonate

3.2.3. Reaction of Diethyl 3-Oxocyclobutanephosphonate under Bucherer-Bergs Conditions

Since attempts at preparing the desired amino nitrile by the Strecker reaction had been unsuccessful, we decided to attempt the synthesis of the spirohydantoin *via* the Bucherer-Bergs procedure. Analysis by ^{13}C and ^{31}P nmr spectroscopy of the crude reaction mixture after diethyl 3-oxo-cyclobutanephosphonate **(134)** was treated with sodium cyanide and ammonium carbonate in aqueous methanol at reflux for 6 hours (Scheme 3.4), indicated that spirohydantoin **(139)** formation had occurred with the ratio of the two isomers being approximately 4:1. This is in accordance with the ratio of products obtained by Bucherer-Bergs reactions on similar substrates.[44, 100]

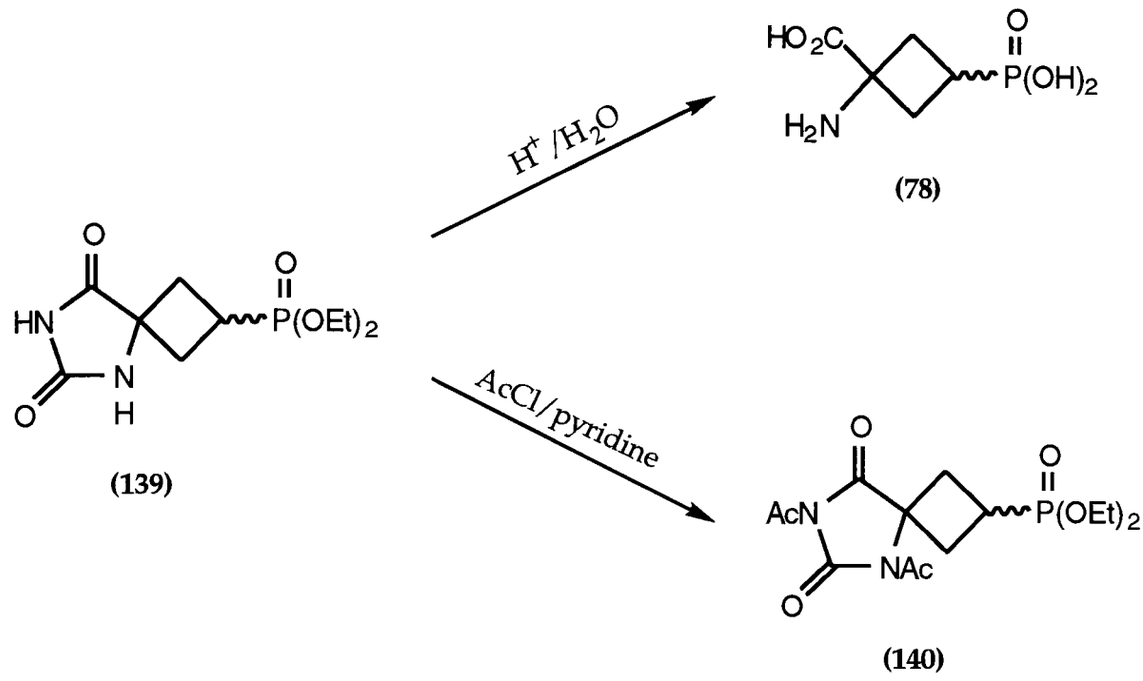


(134)

(139)
65 %
Z:*E* 4:1

Scheme 3.4.

In the case of cyclobutane and cyclopentane compounds separation of the isomers was achieved by ion exchange chromatography and fractional crystallisation, respectively, of the amino acid.[44, 100] Hydrolysis of a sample of the hydantoin **(139)** (Scheme 3.5) and attempts at separation using these methods failed with our amino phosphonic acid **(78)**. Acetylation of the spirohydantoin **(139)**, to give the di-*N*-acetate **(140)** (Scheme 3.5) and analysis of the products by tlc using a variety of solvent systems indicated that the isomers were not separable by silica gel chromatography.



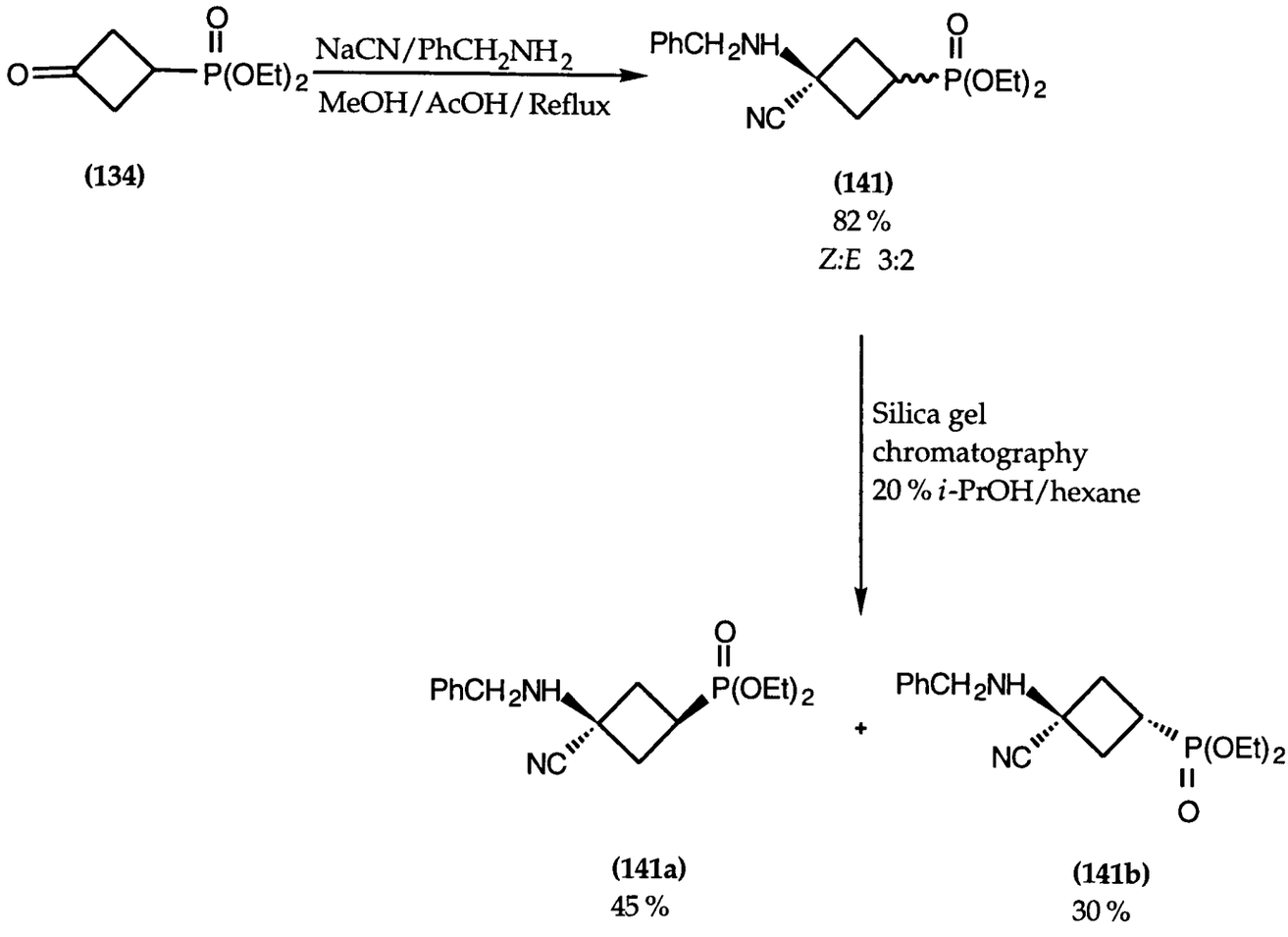
Scheme 3.5.

3.2.4. Synthesis of Diethyl 3-(Benzylamino)-3-cyanocyclobutane-phosphonate

A simple, mild one pot procedure for the synthesis of α-amino nitriles using benzylamine and potassium cyanide in methanol and glacial acetic acid has been described. This reaction proceeds under non-aqueous conditions and the yields appear to be independent of the nature of the substituents on the precursor ketones. This method is reported to give high yields and no by-products.[98]

Reaction of diethyl 3-oxocyclobutanephosphonate **(134)** with benzylamine, sodium cyanide in methanol and acetic acid at reflux for 15 hours (Scheme 3.6) was successful as a method of forming diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141)**. Analysis of the ^{31}P and ^{13}C nmr spectra of the crude reaction mixture indicated the formation of just two products, which were identified as the two isomers (3:2 ratio). Separation of the isomers of diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141)** was more difficult than the separation of the *O*-phenylacetyl **(138)** compound. However, separation can be achieved by

careful silica gel chromatography with hexane and *iso*-propanol as solvent (Scheme 3.6).



Scheme 3.6.

The success of this method of preparing α-aminonitriles is probably due to the stabilising influence of the benzyl group on the intermediate iminium ion. The Strecker reaction proceeds *via* formation of the iminium ion **(142)** followed by attack of this intermediate by the cyanide ion (Figure 3.7). Thus the formation, and hence, stability of this intermediate is of utmost importance to the reaction. The unsubstituted iminium ion **(142a)** formed under standard Strecker reaction conditions is going to be considerably less stable than the benzyliminium ion **(142b)** and thus less likely to form. This allows simple nucleophilic attack of the carbonyl centre by the cyanide ion and subsequent cyanohydrin formation to be the dominant reaction.

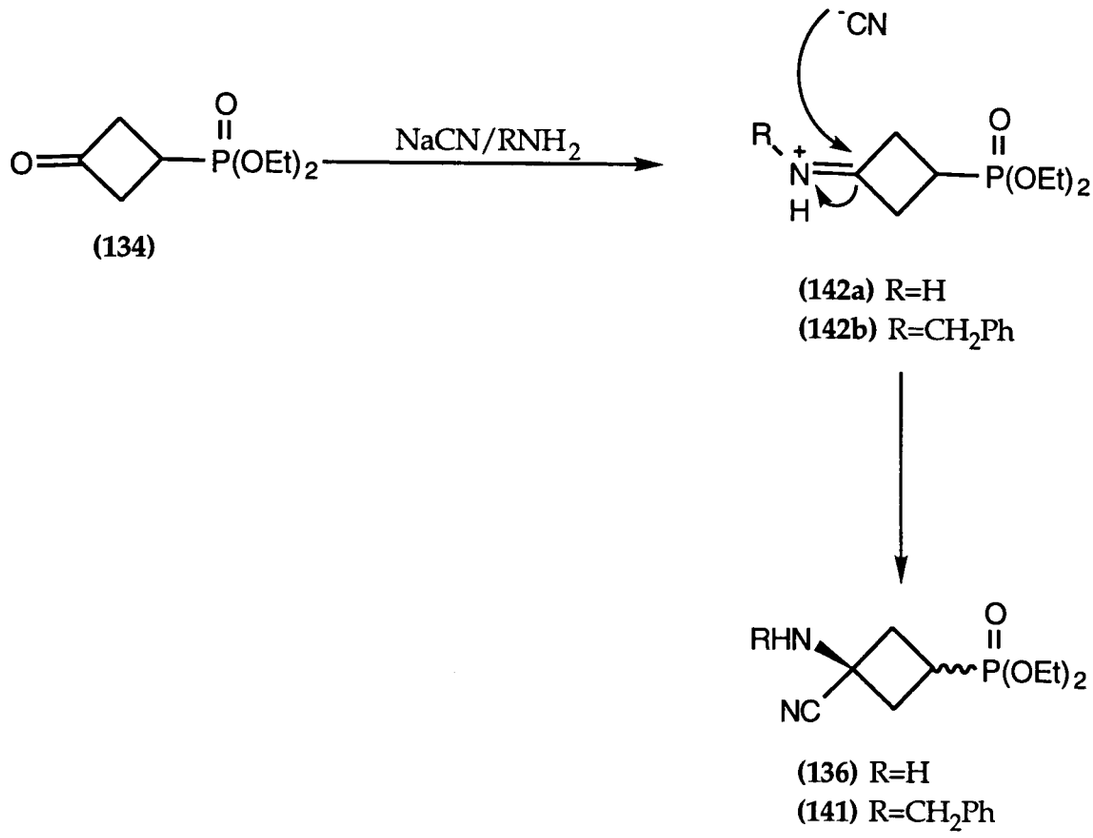


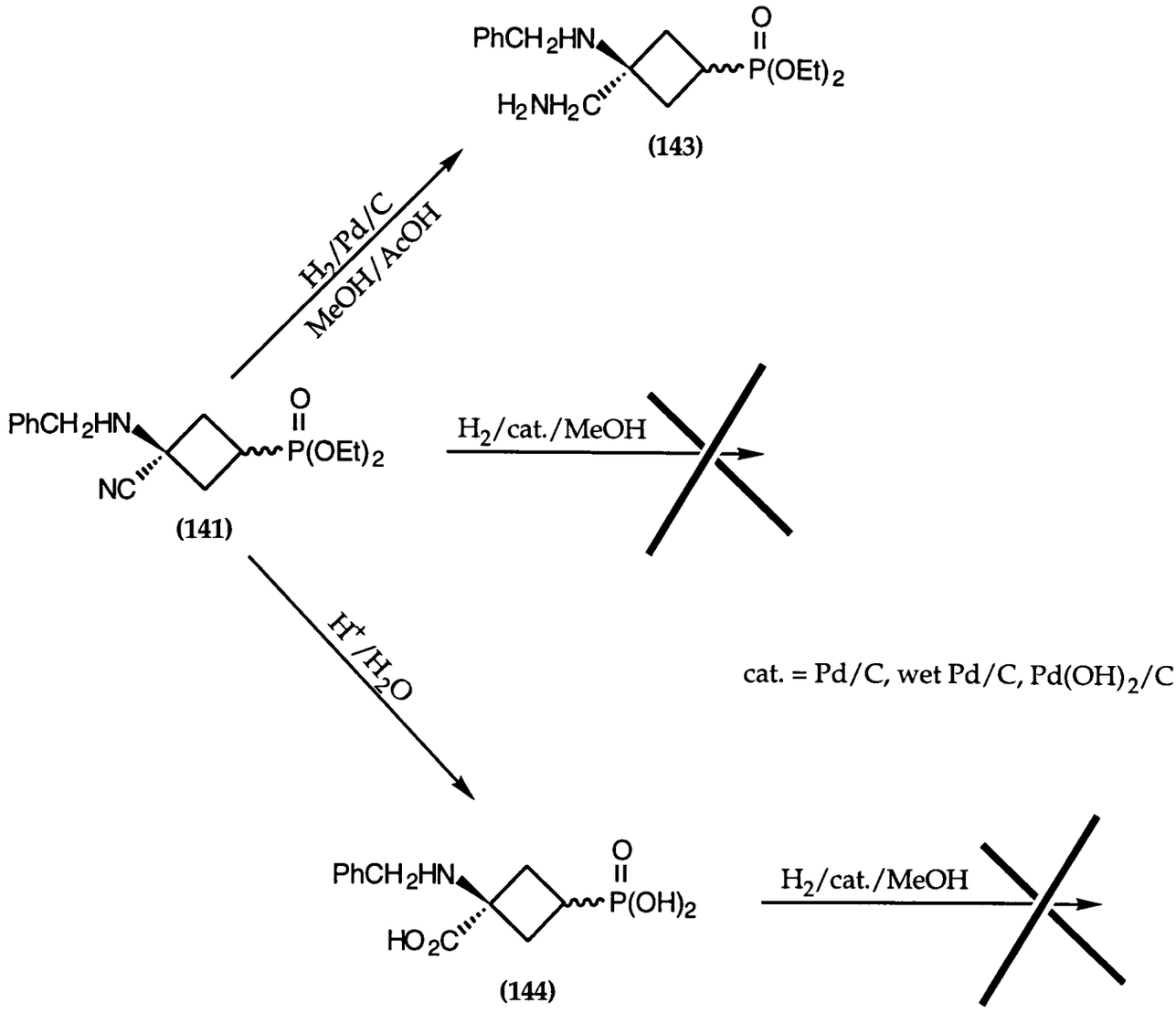
Figure 3.7: Mechanism of the Strecker reaction

The ^{13}C nmr spectrum of the crude reaction mixture of the benzylaminonitrile **(141)** is similar to the ^{13}C nmr spectrum of the *O*-phenylacetylcyanohydrin **(138)** in most respects. The major difference is the position of the signal due to C-3. In the spectra of the *O*-phenylacetylcyanohydrin this signal occurs between 65 and 67 ppm, (depending on the isomer) and in the spectrum of the *N*-benzylamino nitrile the signal due to C-3 occurs between 51 and 53 ppm, this suggests that the amino nitrile has formed in this case rather than the cyanohydrin which has the signal due to C-3 shifted downfield due to the greater electronegativity of the hydroxyl substituent compared to that of the amine substituent. The formation of the benzylaminonitrile was confirmed by infrared spectroscopy which showed absorbances at 2220 cm^{-1}, characteristic of the nitrile group and a strong absorbance at 3273 cm^{-1}, characteristic of the NH of a benzyl amine.[98]

No sign of any cyanohydrin or any unreacted ketone was detected by either nmr or IR spectroscopy.

3.2.4.1 Attempted Removal of the *N*-Benzyl Group

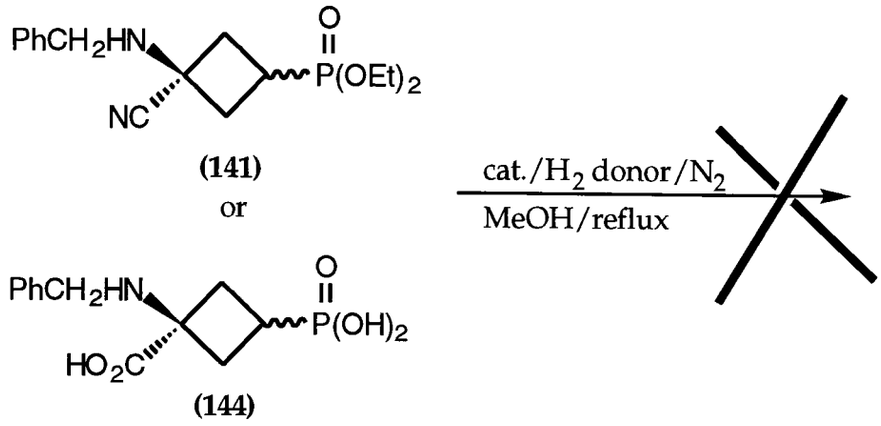
It has been reported that *N*-benzyl groups are easily removed by hydrogenolysis at room temperature and atmospheric pressure in methanol using 5 % palladium on carbon as catalyst, whilst leaving the cyano group untouched. However, under these conditions the benzyl group of our compounds was not removed from either the *Z*- or the *E*-isomer **(141)**. The benzyl group also remained intact after hydrogenolysis over 10 % palladium on carbon in methanol at room temperature at a pressure of three atmospheres (Scheme 3.7). Room temperature hydrogenation at three atmospheres, of diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141)** in methanol and acetic acid using 10 % palladium on carbon as a catalyst resulted in reduction of the nitrile to the amine **(143)**. However, the benzyl group was still left intact. Hydrolysis of the nitrile and concurrent removal of the phosphonate ester groups to give 3-(benzylamino)-3-carboxycyclobutane-phosphonic acid **(144)** and subsequent hydrogenolysis of this compound also failed to deprotect the amine. Other unsuccessful methods for removal of the benzyl group include the use of Pearlman's catalyst (wet $Pd(OH)_2$ on carbon)[101] and wet palladium on carbon, both of which are reported to be effective for removal of benzyl groups. Attempts to remove the *N*-benzyl group using lithium in liquid ammonia resulted in a mixture of unidentified non-cyclobutane products, with no starting material or product isolated.



Scheme 3.7.

Catalytic transfer hydrogenation has been successfully applied as a method for removal of an *N*-benzyl group from a variety of compounds.[102-104] Transfer hydrogenation is reported have greater selectivity and considerably shorter reaction times than traditional hydrogenolysis. Reactions are carried out at atmospheric pressure in the presence of a catalyst (usually palladium on carbon or palladium black) and a hydrogen donor. A number of hydrogen donors have been studied in the removal of benzyl groups, of these ammonium formate[102, 104] and 1,4-cyclohexadiene[103] appear to be the most effective for debenzylation. Attempts to deprotect diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141)** and 3-(benzylamino)-3-carboxy-cyclobutanephosphonic acid **(144)** (Scheme 3.8) with ammonium formate or

1,4-cyclohexadiene in the presence of 10 % palladium on carbon or freshly prepared palladium black were all unsuccessful.



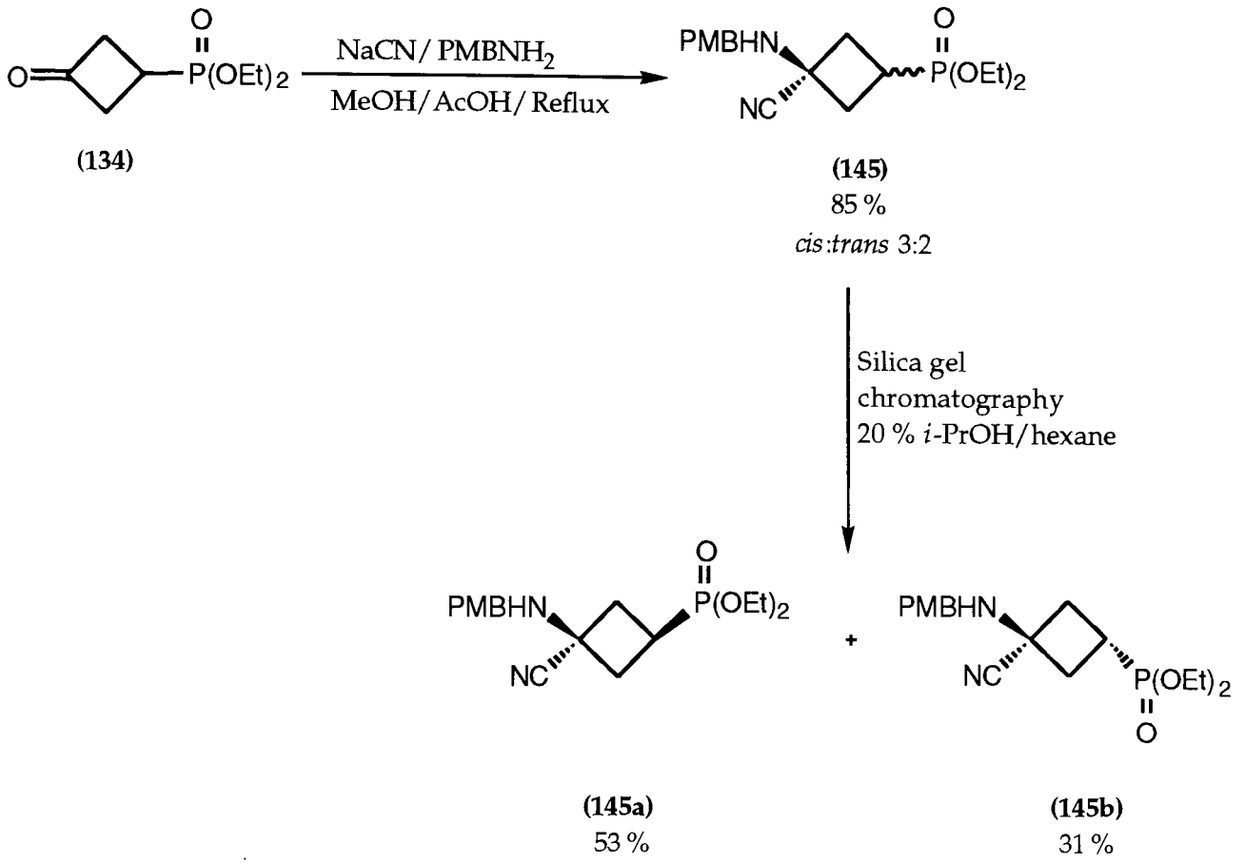
cat. = Pd/C or palladium black
H_2 donor = NH_4HCO_2 or 1,4-cyclohexadiene

Scheme 3.8.

3.2.5. Synthesis of Diethyl 3-(*p*-Methoxybenzylamino)-3-cyano-cyclobutanephosphonate

As it appeared that the *N*-benzyl group could not be removed from *E*- or *Z*-diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate under any reaction conditions, we decided to repeat the Strecker synthesis using *p*-methoxybenzylamine. The *p*-methoxybenzyl (PMB) group has been removed from amines under a variety of mild oxidative conditions, of which the most practical is reaction with ceric ammonium nitrate (CAN).[105, 106]

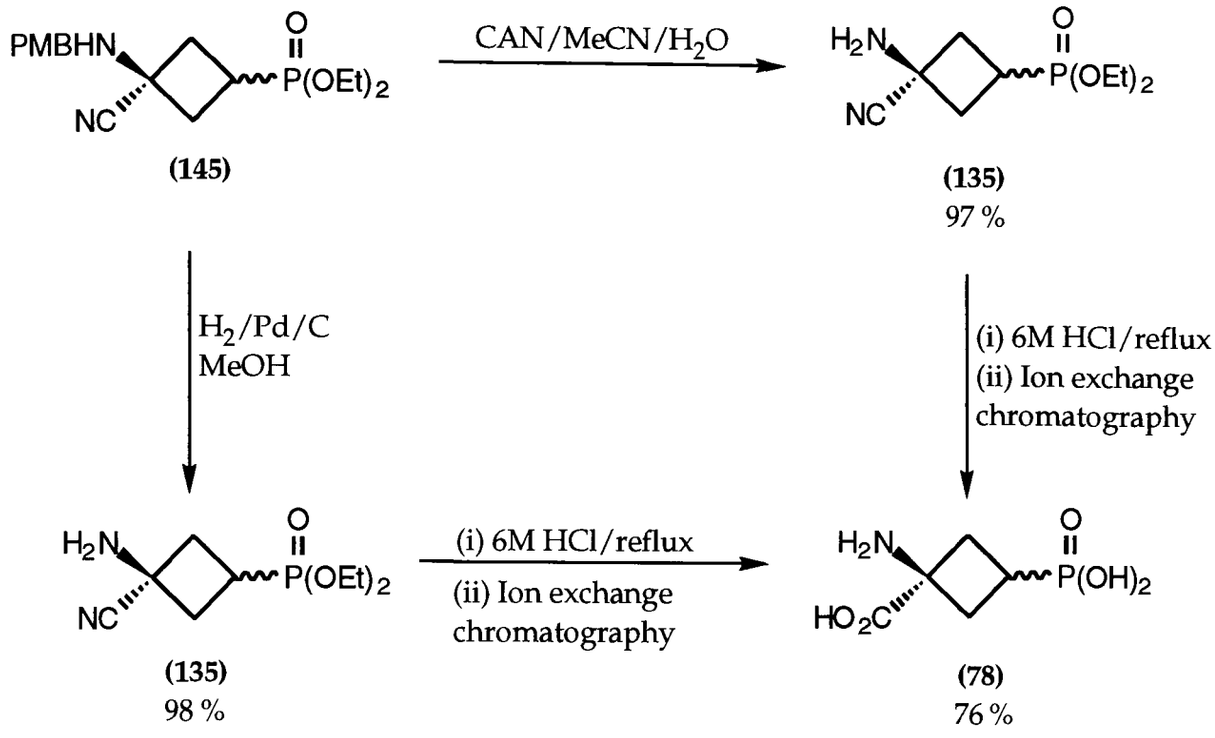
Synthesis of diethyl 3-(*p*-methoxybenzylamino)-3-amino-cyclobutanephosphonate **(145)** (Scheme 3.9) was carried out in a manner similar to, and in comparable yield to that described above for the synthesis of diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141)**. The diastereoisomers were again separated by silica gel chromatography using an *iso*-propanol/hexane solvent mixture.



Scheme 3.9.

3.2.5.1. Removal of the *N*-*p*-Methoxybenzyl Group

The *p*-methoxybenzyl group was removed quantitatively by reaction with CAN in acetonitrile and water (Scheme 3.10). Interestingly, hydrogenolysis over palladium on carbon also facilitated the removal of the *p*-methoxybenzyl group. The crude amino nitriles **(135)** were then hydrolysed to give the amino phosphonic acids **(78)** which were purified by ion exchange chromatography.



Scheme 3.10.

3.2.5.2. Assignment of Configurations of Diethyl 3-(*p*-Methoxybenzyl-amino)-3-cyanocyclobutanephosphonate

The configuration of the isomers was again assigned using ^{13}C nmr spectroscopy and X-ray crystallography of diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutanephosphonate **(145)**. The signal at 121.36 ppm in the ^{13}C nmr spectrum (Figure 3.8) due to the nitrile carbon of the *Z*-isomer **(145a)** is a singlet whereas the signal due to the nitrile carbon of the *E*-isomer **(145b)** (in which the nitrile and phosphonate functionalities are *cis* to one another) at 120.26 ppm is a doublet (J=4.8 Hz) (Figure 3.9) due to the long-range W-coupling of the nitrile carbon to the phosphorus. It is interesting to note that this long-range coupling between the phosphorus and the nitrile carbon is not seen in the ^{13}C nmr spectrum of either diethyl 3-(acetylamino)-3-cyanocyclopentanephosphonate or 3-(*a*cetylamino)-3-cyanocyclohexane phosphonate.[77]

There is a significant difference in the chemical shift of the signal due to C-1 of each of the isomers. The C-1 signal of the *Z*-isomer **(145a)** (23.75 ppm)

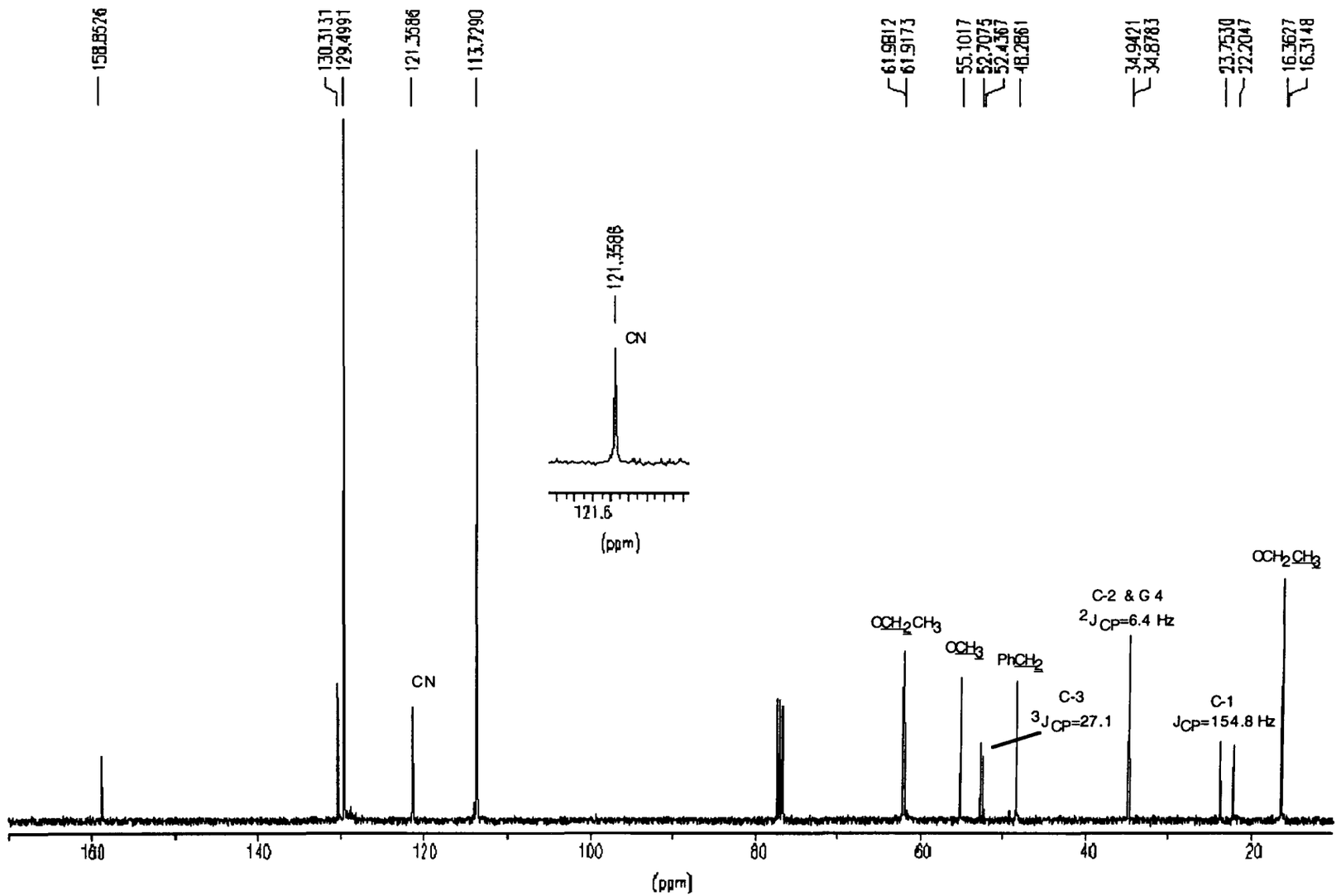


Figure 3.8: ^{13}C Nmr Spectrum of *Z*-Diethyl 3-(*p*-Methoxybenzylamino)-3-cyanocyclobutanephosphonate

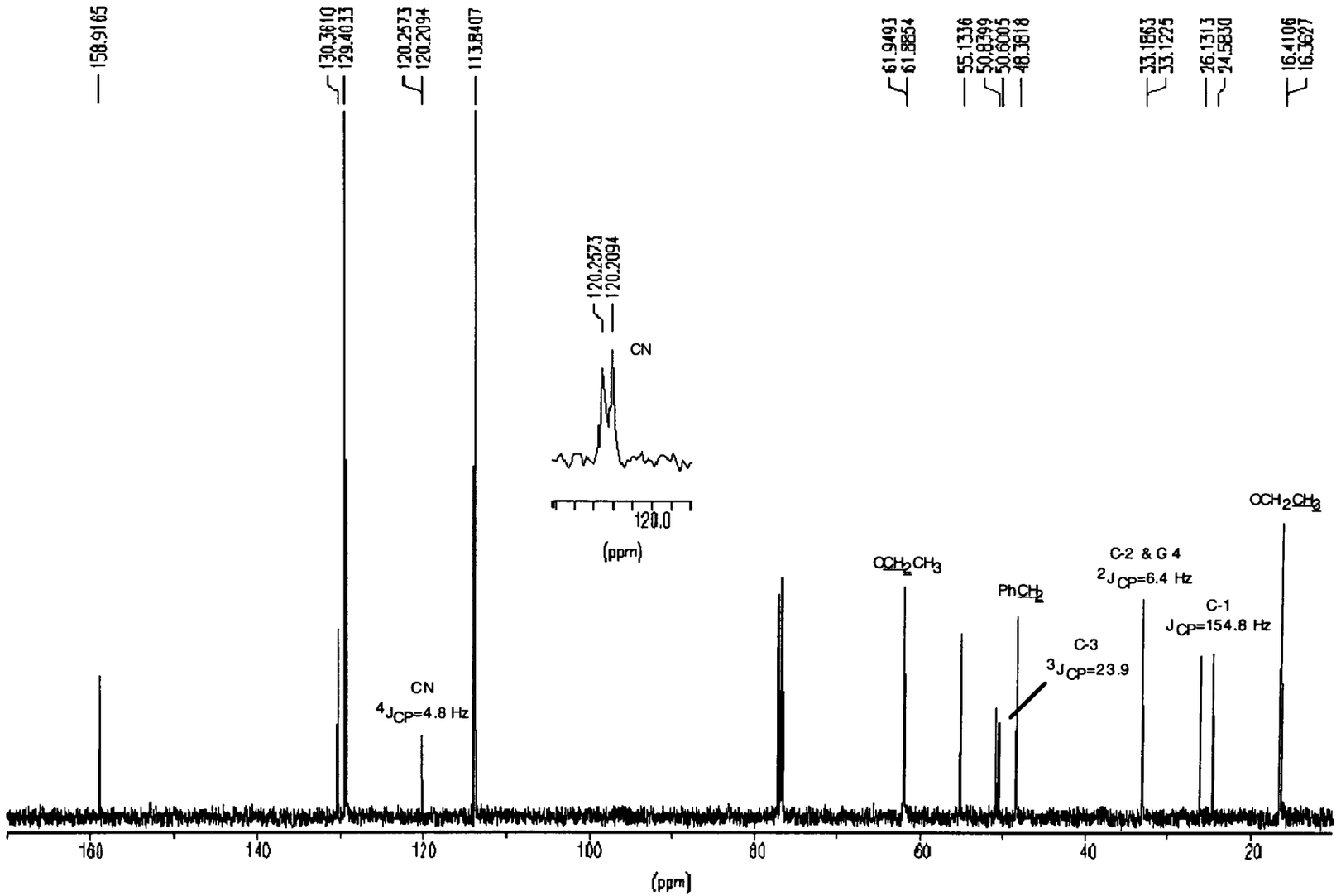


Figure 3.9: ^{13}C Nmr Spectrum of *E*-Diethyl 3-(*p*-Methoxybenzylamino)-3-cyanocyclobutanephosphonate

(Figure 3.8) shows an upfield shift of 2.4 ppm relative to the C-1 signal of the *E*-isomer **(145b)** (26.13 ppm) (Figure 3.9), suggesting that the phosphorus atom of the *Z*-isomer **(145a)** is less electron rich than that of the other diastereoisomer. One possible explanation for this is that an intramolecular hydrogen bond exists between the amine proton and phosphonate moieties. An oxygen atom that is doubly bonded to a phosphorus is known to participate in hydrogen bonding.[107] The phosphonate would be less electron rich if it was donating electrons for a hydrogen bond. Such intramolecular hydrogen bonding would only be possible in the *Z*-isomer in which the amine and phosphonate moieties are *cis* to one another. The signal due to the phosphorus of the *Z*-isomer **(145a)** (29.17 ppm) in the ^{31}P nmr spectrum also shows an upfield shift relative to the *E*-isomer **(145b)** (29.49 ppm).

The *E*-isomer of diethyl 3-(*p*-methoxybenzylamino)-3-cyano-cyclobutanephosphonate **(145b)** was isolated as colourless crystals. Slow recrystallisation from a mixture of ether, toluene and pentane provided crystals suitable for X-ray diffraction. The X-ray structure of *E*-diethyl 3-(*p*-methoxybenzylamino)-3-cyanocyclobutane phosphonate was obtained (Figure 3.10). The dihedral angle C1-C2-C3-C4 is -5.7°, which is considerably less than that of *Z*-diethyl 3-(phenylacetoxy)-3-cyanocyclobutanephosphonate **(138a)**. However, it has been reported that this folding can be significantly affected by solid-state effects, with different crystals of the same compound showing different amounts of ring puckering.[44]

The ^{13}C nmr spectra of the free amino acids **(78)** show similar shifts and coupling constants for the signals due to the cyclobutane ring to those in the spectra of the protected amino nitriles. The signal due to the carboxylic acid functionality of the *E*-isomer at 176.94 ppm is a doublet (J=2.9 Hz) due to the long-range coupling with the phosphorus.

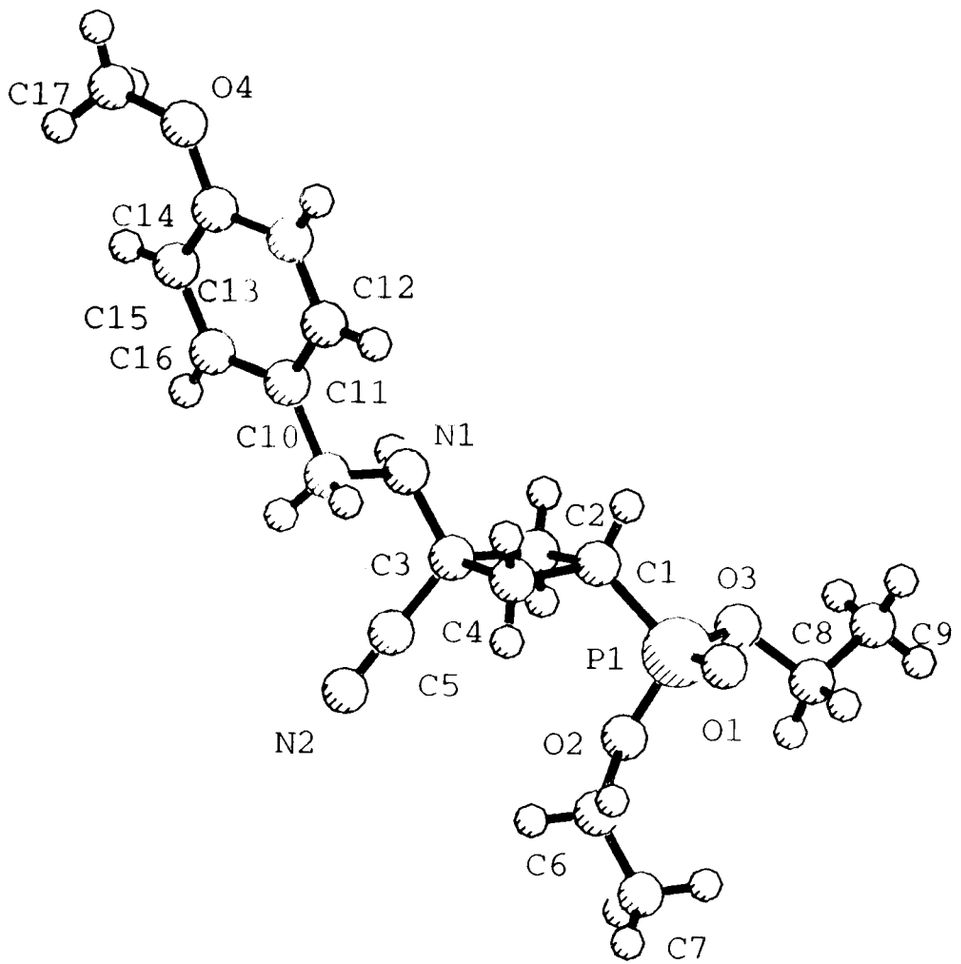
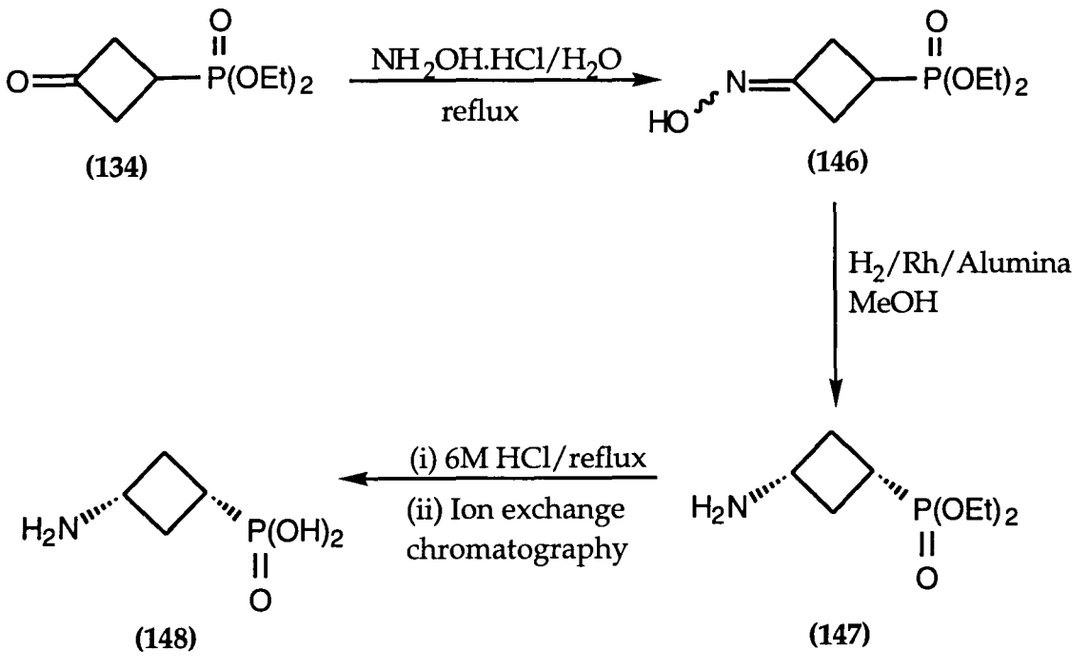


Figure 3.10: Ortep Plot of *E*-Diethyl 3-(*p*-Methoxybenzylamino)-3-cyanocyclobutanephosphonate

3.3. Synthesis of *Z*-3-Aminocyclobutanephosphonic Acid

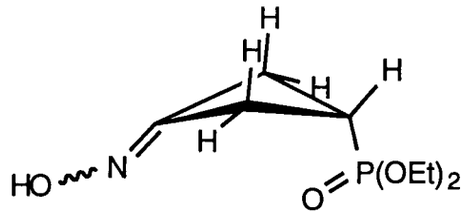
Diethyl 3-oxocyclobutanephosphonate **(134)** can be rapidly converted to 3-aminocyclobutanephosphonic acid **(148)** by a simple synthetic route (Scheme 3.11). Treatment of diethyl 3-oxocyclobutanephosphonate **(134)** with hydroxylamine hydrochloride in water at reflux for 12 hours produces the oxime **(146)** in good yield with a small amount (~10 %) of starting material remaining.[108] The crude oxime **(146)** was converted to the amine by hydrogenolysis at 3 atmospheres of hydrogen with rhodium on alumina as the catalyst. The crude amine **(147)**, contaminated by some diethyl 3-hydroxycyclobutanephosphonate **(134)** was hydrolysed to the amino phosphonic acid **(148)** and purified by ion exchange chromatography (Dowex-50 H^+ form), removing any of the ketone present.



Scheme 3.11.

Only one of the two possible diastereoisomers is formed. This was suggested to be the *Z*-isomer by the following argument. The carbonyl of cyclobutanones is known to prefer to be distorted toward the inner endo face.[109, 110] Thus it is plausible to assume that the oxime **(146)** will adopt a

similar conformation (Figure 3.11). It is also likely that the bulky phosphonate group will prefer to be in the psuedoaxial position to minimise steric interactions. In this conformation it is likely that hydrogenation will occur from the substantially less hindered top side of the cyclobutane ring than from the more hindered bottom side, leading to the Z-isomer.

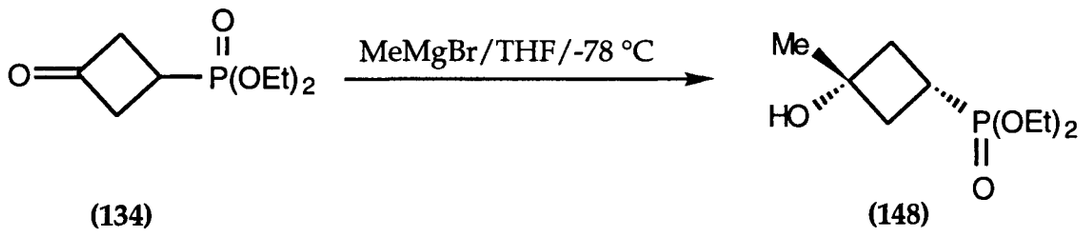


(146)

Figure 3.11: Lower energy conformation of Diethyl 3-hydroxylamine cyclobutanephosphonate

3.4. Synthesis of Diethyl 3-Hydroxy-3-methylcyclobutane-phosphonate

Treatment of diethyl 3-oxocyclobutanephosphonate **(134)** with methylmagnesium bromide at -78 °C results in the formation of only the Z-isomer of diethyl 3-hydroxy-3-methylcyclobutanephosphonate **(149)** (Scheme 3.12). The Z-isomer was identified by the lack of coupling between the methyl carbon and the phosphorus in the ^{13}C nmr spectrum. No evidence of the other diastereoisomer was found.



(134) (148)

Scheme 3.12.

This can be explained in a similar fashion to the formation of only the Z-isomer of diethyl 3-aminocyclobutanephosphonate **(148)**. The lower energy conformation **(134a)** of the cyclobutanone is the one in which the ketone is distorted toward the inner endo-face and the phosphonate is in the pseudoaxial position (Figure 3.12).[109, 110] Molecular modelling studies using Quanta indicate that there is approximately a 4.5 kcal difference between the two possible conformations (60.8 kcal versus 56.3 kcal), indicative of a ratio in the region of 99:1. Thus the nucleophilic attack occurs at the requisite angle (Ø ≈ 110°) from the exo-face to provide a *trans*-selective addition. A similar selective addition has been observed in the addition of (1-phenylvinyl)lithium to a substituted cyclobutanone.[111]

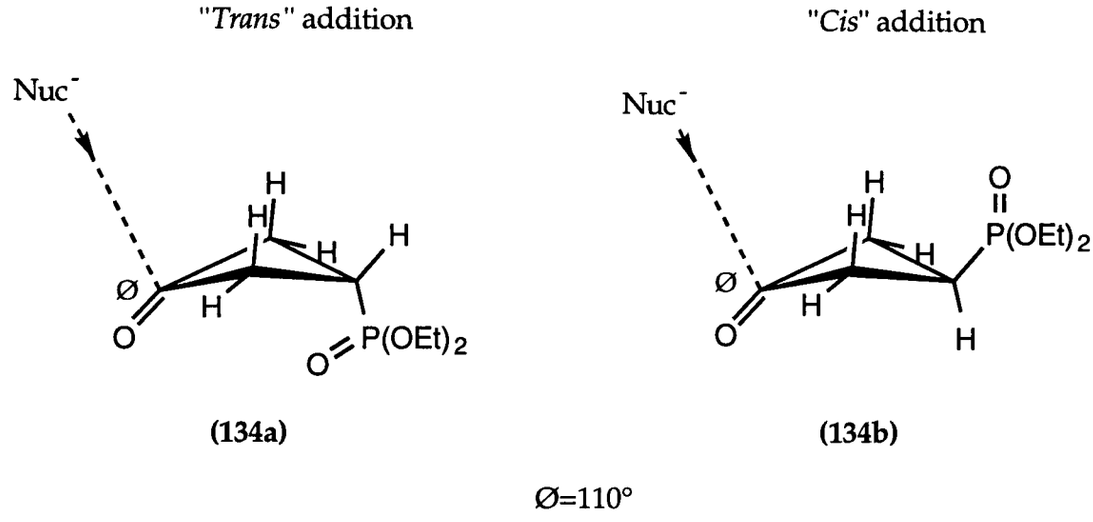


Figure 3.12: Nucleophilic Addition to the Low and High Energy Conformations of Diethyl 3-oxocyclobutanephosphonate

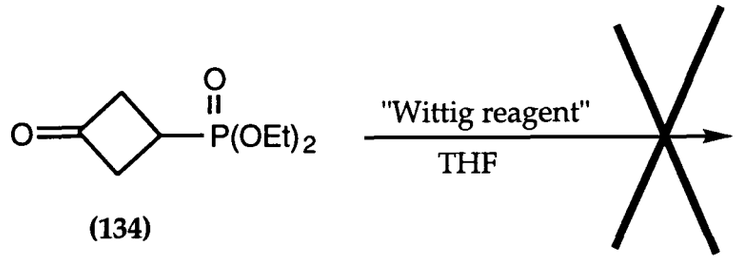
3.5. Homologation of the Ketone Functionality

Diethyl 3-formylcyclobutanephosphonate was investigated as a potential intermediate in the synthesis of homologues of 3-amino-3-carboxy-cyclobutanephosphonic acids **(78)**. Homologation techniques for the formation of aldehydes form a considerable body of methodology. Among these techniques are the Darzen's method and the use of alkoxymethylene-[112] and aryloxymethylene triphenylphosphoranes,[113] diethyl methylthiomethyl-

phosphonate,[114] methoxymethyl diphenylphosphine oxide[115] and α-methoxy-α-trimethylsilyl carbanions.[116] Two major shortcomings are associated with Wittig (and similar) reactions: the first is the unreactivity of some reagents towards various substrates; the second is the formation of side-products from to enolizable ketones.

3.5.1. Attempted Syntheses of Diethyl 3-Formylcyclobutanephosphonate

The lithium derivative of diethyl (1-methylthio)methylphosphonate has been reported as an effective reagent for the conversion of ketones to the homologous aldehydes *via* vinyl sulfide intermediates.[114] The vinyl sulfide intermediates are readily converted to the aldehydes by a mercury(II)-promoted hydrolysis. Reaction of diethyl 3-oxocyclobutane-phosphonate **(134)** with α-lithio diethyl (1-methylthio)methyl phosphonate **(150)** (Scheme 3.13) did not result in the formation of the desired vinyl sulfide. A mixture of starting material and conjugation products were isolated. Similar results were obtained on reaction of diethyl 3-oxocyclobutanephosphonate **(134)** with both diphenyl methoxymethylphosphine oxide **(151)** and diethyl methoxyethoxymethylphosphonate **(152)** (Scheme 3.13).

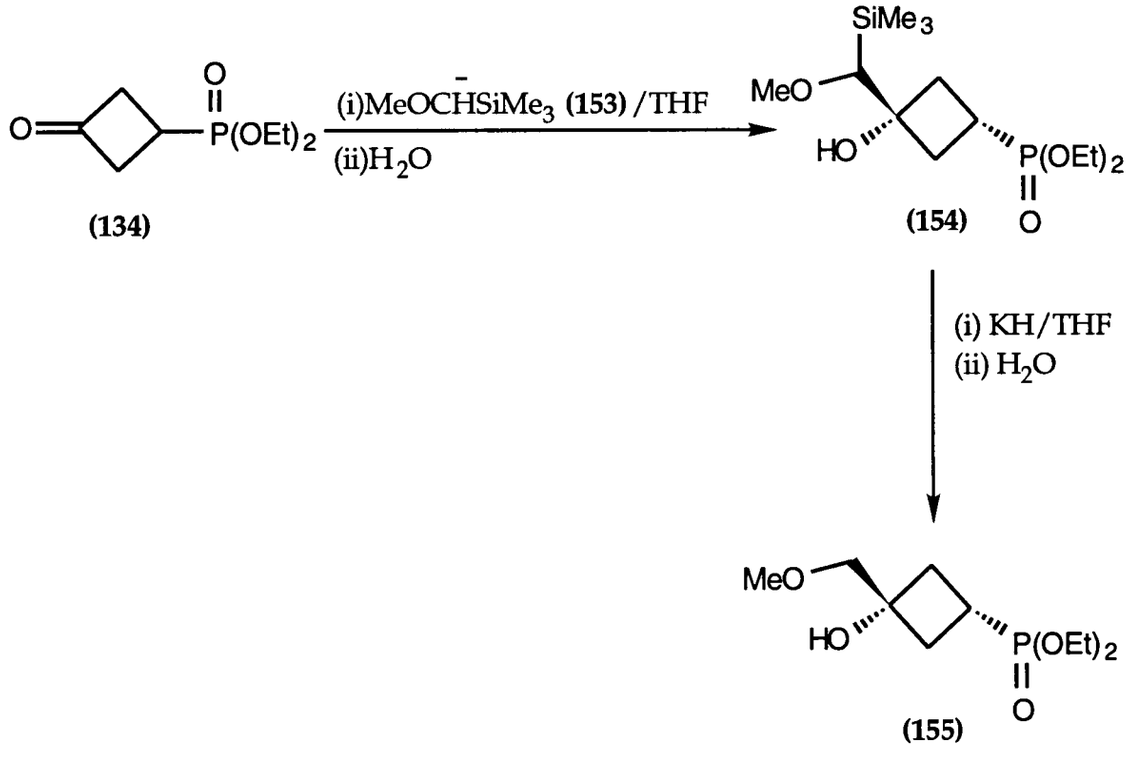


(134)

"Wittig Reagent" =**(150)** $MeSCH_2P(O)(OEt)_2$
(151) $MeOCH_2P(O)(Ph)_2$
(152) $MeOCH_2CH_2OCH_2P(O)(OEt)_2$

Scheme 3.13.

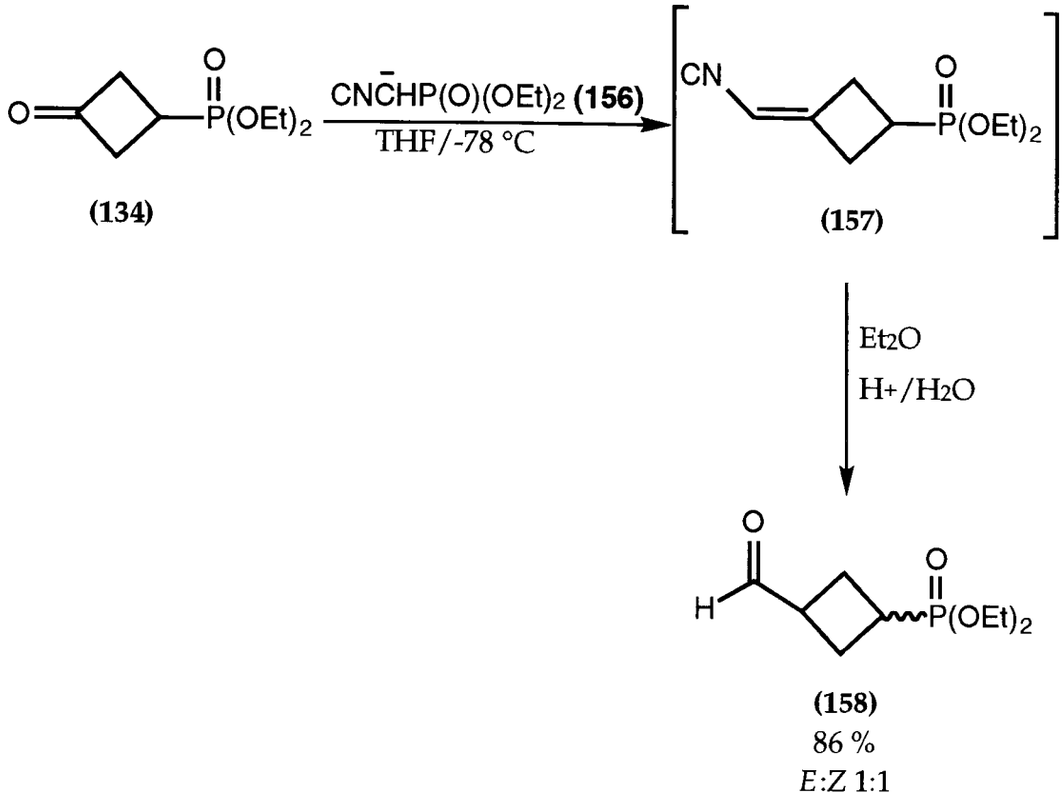
The lithium salt of methoxymethyltrimethylsilane **(153)** has been described as a useful formyl anion equivalent,[116] which is effective in cases where a variety of other Wittig-type reagents are unsuccessful.[117] Treatment of a ketone with the anion of methoxymethyltrimethylsilane **(153)** gives the intermediate alcohol, which does not immediately undergo syn-elimination of -$OSiMe_3$ *in situ*, but upon treatment with potassium hydride in tetrahydrofuran at room temperature, leads to the corresponding enol ethers. Treatment with formic acid gives the aldehydes in high yields.[116] Reaction of the lithium salt of methoxymethyltrimethylsilane **(153)** with diethyl 3-oxocyclobutanephosphonate **(134)** results in the formation of the intermediate alcohol **(154)** (Scheme 3.14). However, reaction of this intermediate with potassium hydride at room temperature or in refluxing tetrahydrofuran yields only the β-methoxy alcohol **(155)**. Again, only one of the possible diastereoisomers is formed. Presumably, reaction with potassium hydride results in a 1,3-migration of the silicon functionality. However, no elimination occurs and the silyloxy group is then hydrolysed in the work up.



Scheme 3.14.

3.5.2. Synthesis of Diethyl 3-Formylcyclobutanephosphonate

The anion of diethyl isocyanomethylphosphonate **(156)** reacts with aldehydes and ketones *via* a Wittig-Horner reaction to form α,β-unsaturated isocyanides which can then be hydrolysed to give homologous aldehydes containing one extra carbon atom. Since the reaction between cyclobutanone and the lithium salt of diethyl isocyanomethylphsophonate **(156)** was successful,[118] this appeared to be a promising Wittig reagent for reaction with our phosphonate substituted cyclobutane. Diethyl 3-oxocyclobutane-phosphonate **(134)** was treated with α -lithio diethyl isocyanomethylphosphonate **(156)** in tetrahydrofuran at -78-0 °C for approximately 2 hours (Scheme 3.15) after which time the reaction was quenched with water and the tetrahydrofuran was removed. The residue was redissolved in diethyl ether, 6M hydrochloric acid was added and the reaction stirred at room temperature for 12 hours. The reaction was carried out in tetrahydrofuran due to the low solubility of the phosphonate in diethyl ether. However, when the hydrolysis of the intermediate unsaturated isocyanide **(157)** is carried out in tetrahydrofuran the resulting aldehydes have a tendency to trimerise, hence the redissolution in ether.[118] Diethyl 3-formylcyclobutanephosphonate **(158)** was isolated in good yield as a 1:1 mixture of the two isomers as determined by ^{31}P nmr.



Scheme 3.15.

Extensive analysis of the isomeric mixture of aldehydes **(158)** by tlc indicated that it would not be possible to separate the two isomers by chromatography. As the mixture was otherwise extremely pure, we decided to proceed to the next stage, when separation of the diastereoisomers was likely to be more facile.

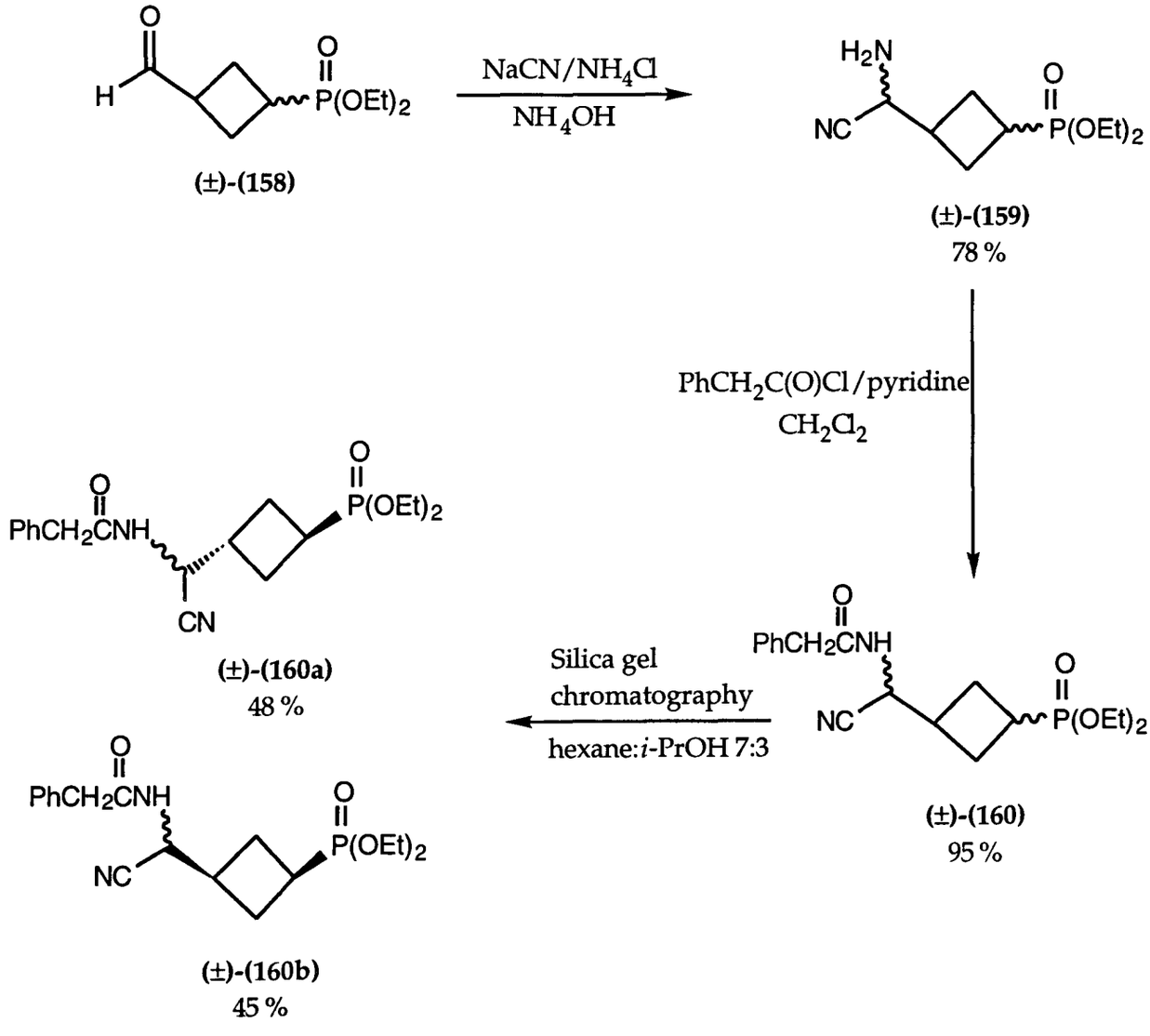
3.6. Synthesis of 3-(Amino-carboxymethyl)cyclobutane-phosphonic Acid

3.6.1. Synthesis of Diethyl 3-(Phenylactetylamino)-cyanomethyl)-cyclobutanephosphonate

Reaction of diethyl 3-formylcyclobutanephosphonate **(158)** with sodium cyanide and ammonium chloride in aqueous methanol resulted in the formation of large amounts of undesired condensation products. However, reaction of the aldehyde **(158)** (Scheme 3.16) with sodium cyanide and ammonium chloride in ammonium hydroxide for 12 hours, with light

excluded, produced a high yield of the desired amino nitrile **(159)**. Little or no formation of condensation products occurred under these conditions. Longer reaction times resulted in hydrolysis of the phosphonate esters.

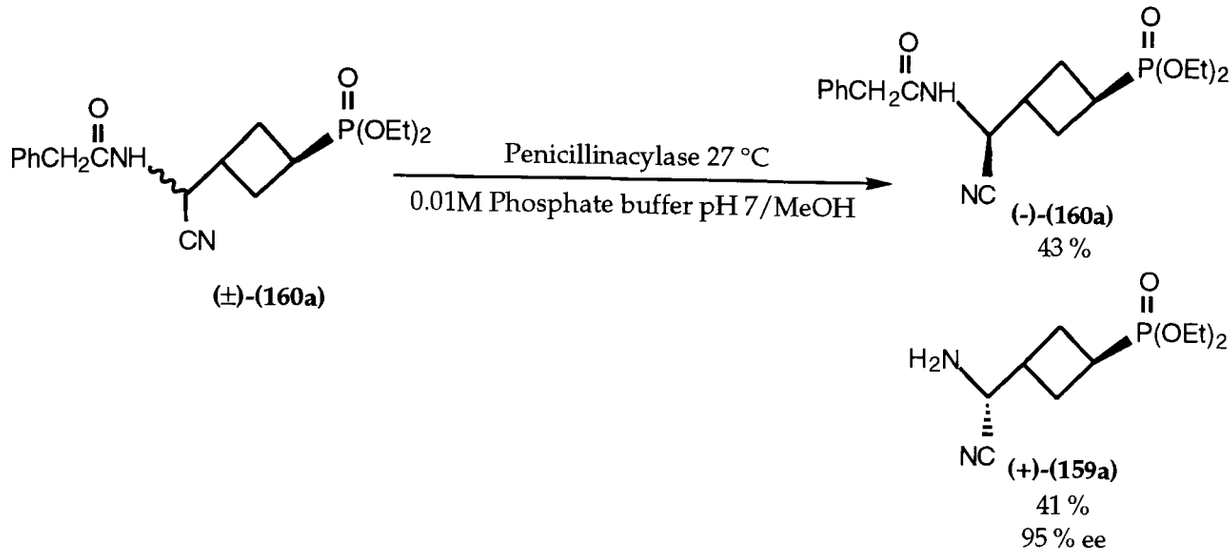
As it was hoped that the enantiomers of these compounds could be separated by enantioselective enzymatic hydrolysis the amino nitriles were converted to the *N*-phenylacetyl derivatives **(160)**. The diastereoisomers were easily separated by silica gel chromatography using *iso*-propanol and hexane as a solvent mixture. The assignment of the isomers was again made using the characteristic coupling of the phosphorus to the carbon attached to the C-3 position of the *Z*-isomer, which was found to be the second isomer that eluted from the column.



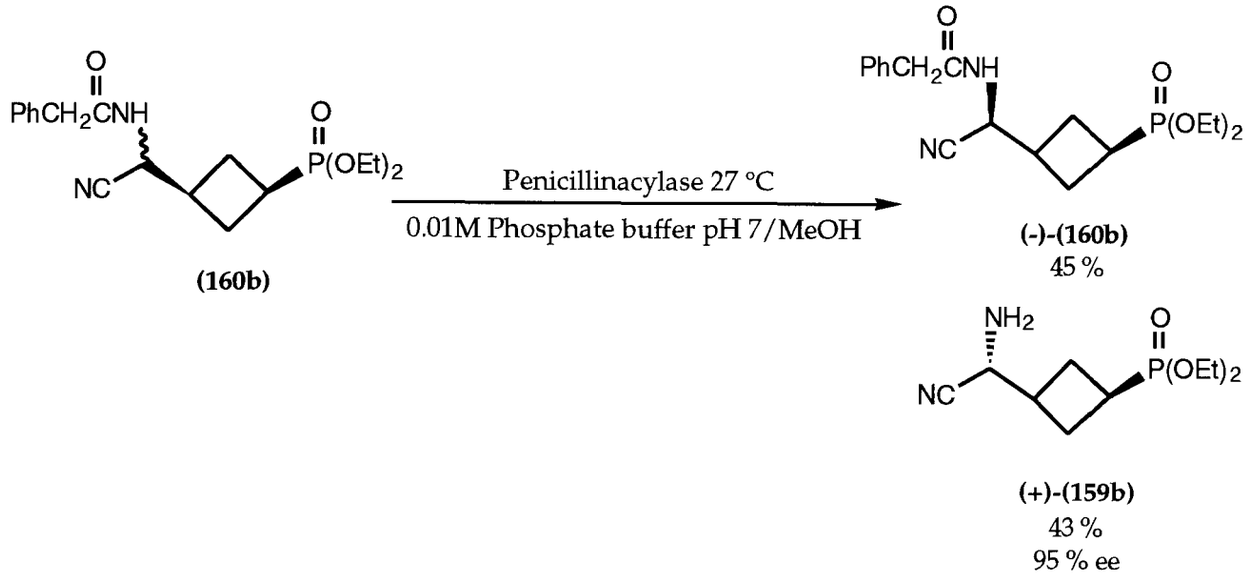
Scheme 3.16.

3.6.2. Enzymatic Separation of Enantiomers

There are two general approaches to the synthesis of optically active amino acids: asymmetric synthesis of enantiomers and the resolution of racemates by chemical or enzymatic means. Of these methods, resolution of a racemate using enzymatic hydrolysis is a mild, highly enantioselective method that procedes with good yields. Penicillinacylase (EC 3.5.1.11) from *Escherichia coli* is known to show *L* directed stereochemical preference in the hydrolysis of phenylacetylamino acids. Further investigation has shown that penicillinacylase is capable of hydrolysing a variety of phenylacetylamino compounds, including phenylacetylamino nitriles.[119] A number of 1-aminoalkylphosphonic acids have been prepared with high enantioselectivity *via* penicillinacylase catalysed hydrolysis of the phenylacetylamino phosphonic acids.[120] These studies indicate that penicillinacylase has a high substrate tolerance and would thus be of use in the resolution of the enantiomers of (±)-*E*- and (±)-*Z*-diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutanephosphonate. Enzymatic hydrolyses of the racemic phenylacetylamino nitriles (Scheme 3.17 and scheme 3.18) were carried out using penicillinacylase immobilised on Eupergit under the conditions described by Rossi.[119] The reactions were monitored by tlc until there ceased to be an obvious increase the amount of phenylacetic acid produced, (approximately 6 hours). Acidification of the reaction mixture to pH 4 with 6 M hydrochloric acid followed by extraction with dichloromethane yielded the unhydrolysed phenylacetylamino nitrile. Neutralisation of the aqueous layer and re-extraction with dichloromethane yielded the hydrolysed aminonitrile.



Scheme 3.17.



Scheme 3.18.

The absolute configuration of the isomers is not known. However, it is likely that the isomer hydrolysed by the enzyme has *R* stereochemistry. Penicillinacylase is known to preferentially hydrolyse the *L*-isomer of amino acids and extensive efforts have been made to determine factors that influence the stereoselectivty of the hydrolysis of other phenylacetylamino compounds.[119] These studies have shown that when a nitrile, rather than a carboxylic acid functionality, is present on the carbon α to the phenylacetylamino group and the third substituent is larger than an ethyl

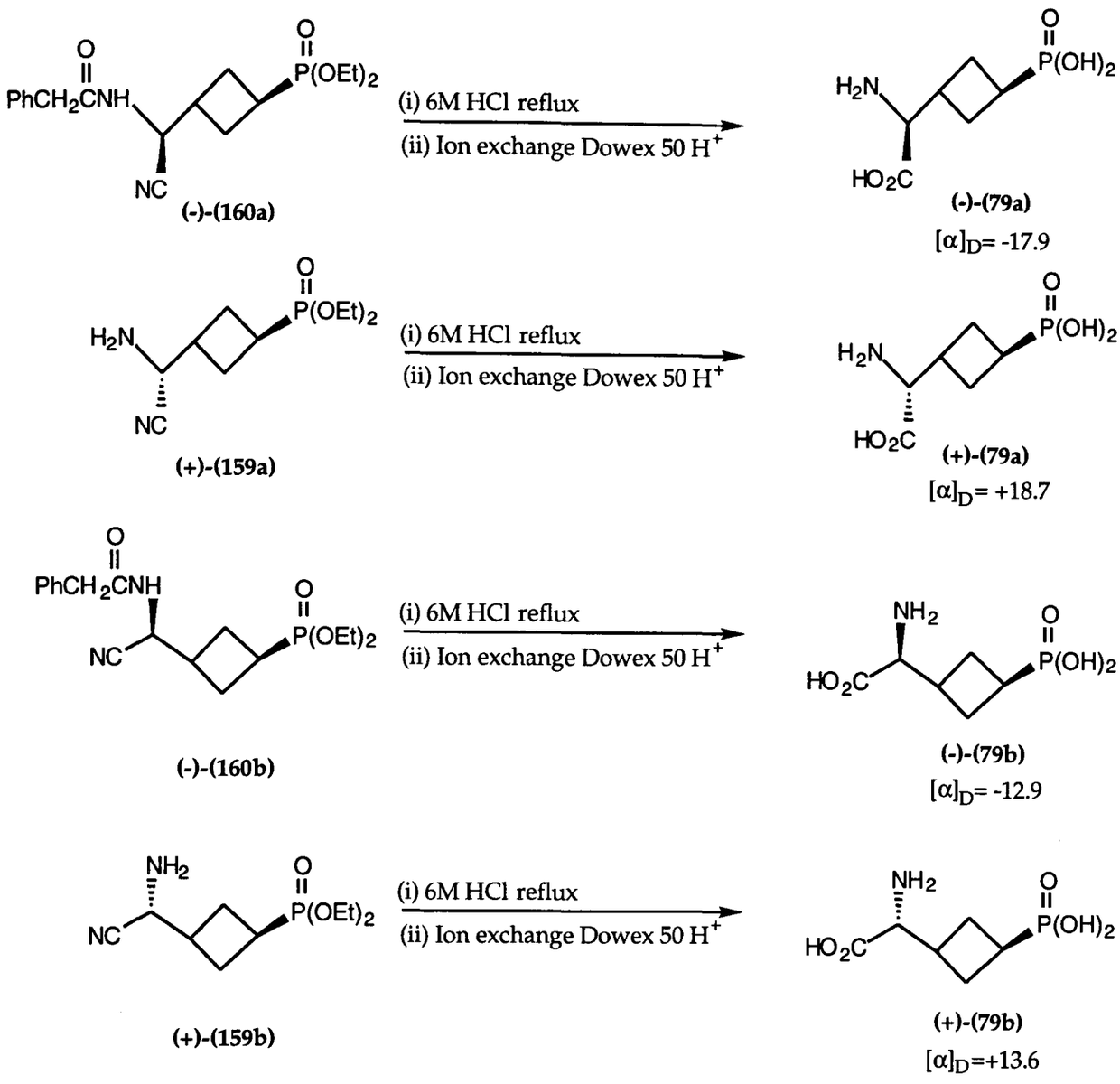
group for example, an *iso*-propyl or phenyl group, then the *R*-isomer is the one which is preferentially hydrolysed. As the cyclobutane ring can be thought of as *iso*-propanol group that has a bond between the two methyl groups, then it is plausible to expect a similar stereoselectivity in the the hydrolysis of these cyclobutane compounds.

3.6.3. Determination of Enantiomeric Excesses

The enantiomeric purities of the compounds were determined by ^{19}F nmr analysis of the Mosher's amides.[121] Reaction of samples of the hydrolysed isomer with α-methoxy-α-trifluoromethylphenylacetyl chloride provided the Mosher's amide of the amino nitrile. On comparison of the ^{19}F nmr spectrum of the single enantiomer from the enzymatic hydrolysis with the ^{19}F nmr spectrum of a sample of the Mosher's amide of the racemic compound, no evidence of a signal in the ^{19}F nmr spectrum corresponding to the opposite enantiomer was found in either of the two diastereoisomers. However, given that the sample converted to the Mosher's amide was in the region of 3-4 mg, it would be unwise to say that the enantiomeric purity was greater than 95 %.

3.6.4. Synthesis of 3-(Amino-carboxymethyl)cyclobutanephosphonic Acids

The amino nitriles **(159)** and phenylacetylamino nitriles **(160)** were treated with 6 M hydrochloric acid at reflux to produce the aminophosphonic acids as their hydrochloride salts (Scheme 3.19). Purification of the aminophosphonic acids by ion exchange chromatography (Dowex 50W, H^+ form) provided the enantiomerically pure aminophosphonic acids **(79)**.



Scheme 3.19.

3.7. Conclusion

The key intermediate diethyl 3-oxocyclobutanephosphonate **(134)** has been used in the synthesis of a variety of cyclobutane phosphonic amino acids. Both diastereoisomers of 3-amino-3-carboxycyclobutanephosphonic **(78)** acid have been prepared *via* a modified Strecker reaction. In the synthesis of 3-amino-cyclobutanephosphonic acid **(149)**, the cyclobutane phosphonic acid analogue of γ-aminobutyric acid (GABA), only the *Z*-isomer was obtained due to a diastereoselective hydrogenation of the intermediate hydroxylamine. The synthesis of *E*- and *Z*-diethyl 3-formylcyclobutanephosphonates **(158)** was also carried out and the products were transformed into *E*- and *Z*-3-(amino-

carboxymethyl)cyclobutanephosphonic acid **(79)** , the homologue of 3-amino-3-carboxycyclobutane-phosphonic acid **(78)**. In all cases the diastereoisomers were separable by column chromatography. The enantiomers of 3-(amino-carboxymethyl)cyclobutanephosphonic acids **(79)** were separated by enantioselective enzymatic hydrolysis of the intermediate diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutanephosphonates **(160)**. Using this method of resolution, high enantioselectivities were obtained. Thus diethyl 3-oxocyclobutanephosphonate **(134)** is a versatile intermediate in the synthesis of cyclobutane phosphonic acid analogues of amino acids.

Chapter 4

Synthesis of Cycloalkane 1-substituted-1-phosphonate Compounds *via* Phase-transfer Catalysed Alkylations

4.1. Introduction

4.1.1. Development of Antiviral Agents

Extensive efforts have been made in recent years to develop drugs for the safe and effective treatment of viral diseases. However, the concept of selective toxicity, in which a treatment destroys an infection but is not injurious to the host has met with only limited success in the treatment of viral infections. This is largely due to the close relationship between the host organism and the invading virus.

Viral infections differ in two respects from bacterial and fungal infections. The virion is entirely dependent on the host cells' biochemical machinery and the genetic material of the virus can exert its control on the host cell so as to wholly or partially divert its metabolism to the production of viral nucleic acid and viral protein. Hence viruses can not reproduce outside the host cell. They are completely dependent on the host cell for their energy and synthetic requirements.

Viruses contain either RNA or DNA but not both. It is convenient to classify viruses according to the type of nucleic acid they contain. DNA viruses include Epstein-Barr virus, herpes viruses and hepatitis (both A and B) virus. Common RNA viruses include influenza, rhinovirus and polio virus. There is a third class of viruses, known as retroviruses. These contain RNA that is transcribed into a DNA hybrid which then serves as a template for the synthesis of double-stranded DNA which is integrated into cellular DNA prior to multiplication. This class of virus includes the human immunodeficiency

virus (HIV), which is the etiologic agent of acquired immune deficiency syndrome (AIDS).

4.2. The Viral Life Cycle

The exact replication cycle of a virus depends on the class of virus. However, the general replication cycle proceeds as follows. A virion becomes attached to the outside of the cell and penetrates the cell membrane. The protein coat of the virion is removed by lipases and peptidases and the viral nucleic acid is transported to its replication site. The virion now takes control of the host cells' nucleic acid and protein synthesis. A mRNA copy of the viral genome is synthesised (transcription), from which the viral proteins are synthesised on the cellular ribosomes (translation). The viral nucleic acid is replicated. The new viral proteins and nucleic acids are assembled into virions and the host cell finally ruptures to liberate large numbers of virions so that further infection occurs.

Two additional features of the virus host interaction are latency and transformation. DNA copies of the genome of herpes viruses and oncoviruses are incorporated into the host's chromosomes and are replicated with them in perpetuity. Emotional or environmental factors can reactivate the latent gene and cause a new outbreak of disease, e.g. cold sores (herpes simplex virus) and the onset of acquired immunodeficiency syndrome (AIDS) from the HIV virus. Oncoviruses may lead to the transformation of the cell into a malignant cell, resulting in cancer.[122]

4.3. Herpes Viruses

The group of human herpes viruses include herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), cytomeglavirus (CMV), and Epstein-Barr virus (EBV). These are all large, enveloped DNA viruses which share the unique characteristic of becoming latent in the body after a primary

infection and having the potential for subsequent reactivation after varying periods of time.[122]

4.3.1. Herpes Simplex Virus

Herpes simplex viruses are of two types, both of which are found worldwide, with humans as their only natural reservoir. Since the virus can not remain infectious for long outside the human body, direct contact with secretions is necessary for transmission of the virus. Generally HSV-1 is transmitted in oral secretions and is responsible for cold sores and herpes keratitis where as HSV-2 is transmitted genitally.[122]

Once transmission has occured, it is thought that the herpes virus particles enter the cell *via* fusion of the viral membrane with the plasma cell membrane and encorporation of naked nucleocapsids into the cytoplasm. One or more of the glycoproteins on the herpes virus envelope are thought to be responsible for this fusion which results in the formation of giant syncytia. Once the parental DNA is uncoated, it moves rapidly to the nucleus of the host cell where it begins replication after about four hours. Assembly of herpes virus nucleocapsid takes place in the nucleus of the cell. The enveloped herpes virus particles are transported through the cytoplasm and are released from the plasma cell membrane.[122]

4.4. Antiviral Chemotherapy

The intimate relationship between host cell and virus makes it difficult to find a substance which inhibits or destroys the virus without being toxic to the cell. Many classes of compounds have been investigated for antiviral activity. However, the number of compounds in clinical use remains very small. After ten years of intensive research into viruses in the wake of the acquired immune deficiency syndrome (AIDS) epidemic, there are still only a

relative handful of antiviral drugs in routine clinical use. This contrasts starkly with the vast range of antibacterial drugs currently available.

It is important to recognise that many antiviral agents, including some that are in clinical use, have more than one apparent mechanism of action. Thus the issue of defining exactly which mechanism is antiviral and which is causing a toxic reaction can be difficult to determine.[123] There are still only a few antiviral drugs licensed for regular clinical use (Table 4.1).

Table 4.1: Licensed Antiviral Drugs[124]

Step in the Viral Life Cycle	Antiviral Agent	Virus
Attachment	Deoxynojirimycin	HIV-1
Penetration	Amantadine	Influenza A
Uncoating	Amantadine and Rimantadine	Influenza A
Replication		
(DNA)	AZT	HIV-1
	ddI	HIV-1
	Acyclovir	HSV & VZV
	5-Iodo-2'-deoxyuridine	HSV
	5-Trifluoromethyl-2'-deoxyuridine	HSV
	Adenine arabinoside	HSV
	5-Ethyl-2'-deoxyuridine	HSV (Germany)
	5-Iodo-2'-deoxycytidine	HSV (France)
(RNA)	Ribavirin	Respiratory syncytial virus

Two lipid soluble primary amines (Figure 4.1), amantadine **(161)** and rimantadine **(162)** are well established in the treatment of influenza. Amantadine **(161)** has been licensed for use in the USA since 1966 and rimantadine is available for clinical use in the former USSR.[125,126] In high concentrations these compounds exert a non-specific activity which prevents viral penetration. In lower concentrations (0.1-0.5 μM), they appear to prevent stages involved in either penetration or virus assembly.[127]

(161) (162)

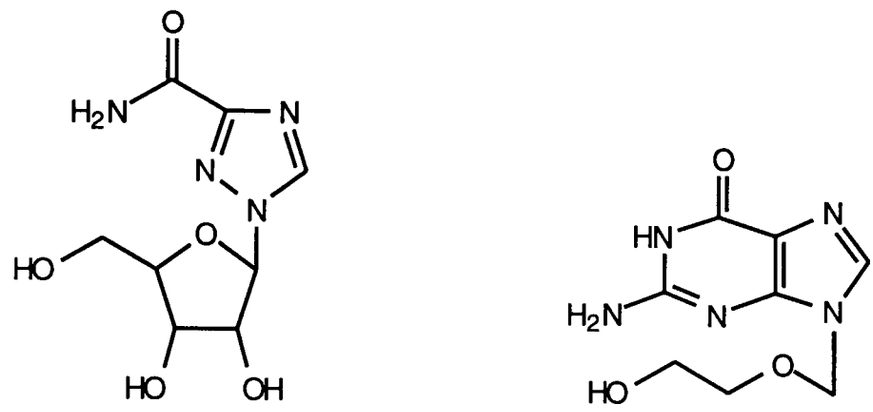
Figure 4.1: The Structure of Amantadine and Rimantadine

However, the clinical use of amantadine **(161)** has been restricted for several reasons. It is only really effective against enveloped viruses such as influenza and has side effects such as insomnia and hallucinations resulting from secondary effects on the central nervous system. Rimantadine **(162)** is reportedly more effective than amantadine **(161)** against influenza[128] and also demonstrates reduced side effects.[129]

4.4.1. Nucleoside Analogues

Ribavirin **(163)** (Figure 4.2) exhibits a broad spectrum of activity against a range of viruses, including influenza, both *in vitro* and *in vivo.* [130, 131] It is known to inhibit the synthesis of viral mRNA in influenza. The active species *in vivo* is thought to be ribavarin 5'-*O*-triphosphate which is known to be an inhibitor of influenza virus RNA polymerase *in vitro* under conditions in which ribavirin and ribavirin 5'-*O*-monophosphate have no activity.[132] However, the clinical use of ribavirin is limited due to its teratogenicity.

Most of the nucleoside analogues which have promise as antiviral agents act by interrupting nucleic acid synthesis. One of the most successful and effective nucleoside antiviral drugs is 9-(2-hydroxyethoxymethyl) guanine (acyclovir) **(164)**. [133] Acyclovir is used for the treatment of herpes viruses.

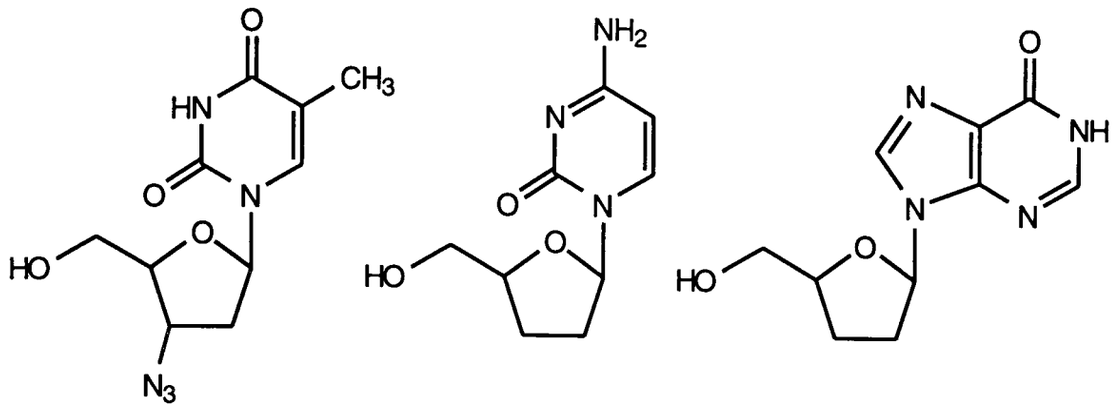


(163) (164)

Figure 4.2: The Structure of Ribavirin and Acyclovir

Acyclovir **(164)** has low toxicity as it is only metabolised by cells that are infected with the herpes viruses, where it has a much higher affinity for the virus induced deoxythymidine kinase than for the corresponding kinase of the host cell. This enzyme phosphorylates the acyclovir, forming acyclovir monophosphate which is further phosphorylated to the triphosphate. Once again the DNA polymerase has a much higher affinity for acyclovir triphosphate than the cellular polymerase; hence it is added to viral DNA in preference to cellular DNA. Once the drug is incorporated in to the DNA it acts as a chain terminator due to the lack of a 3'-hydroxyl group. Furthermore, it is also known to act as a suicide substrate for the DNA polymerase.[134, 135]

In recent years, many nucleoside analogues (Figure 4.3) have been prepared in the hope that they will act as inhibitors of the reverse transcriptase enzyme of the HIV virus. These compounds act by competing as substrates with the normal nucleoside substrates. The most potent of these nucleoside analogues are 3'-azido-2',3'-dideoxythymidine (AZT) **(165)**,[136] 2',3'-dideoxycytidne (ddC) **(166)**[137] and 2',3'-dideoxyinosine (ddI) **(167)**[138].



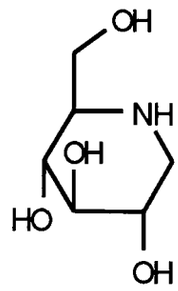
(165) (166) (167)

Figure 4.3: The Structure of Some Nucleosides with Antiviral Activity

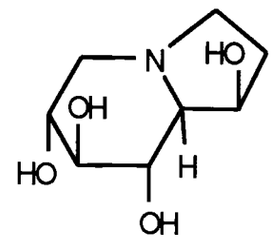
The nucleosides must first be converted intracellularly to the corresponding 5'-*O*-triphosphate before any interaction with reverse transcriptase can occur. There is no difference in the ability of uninfected and virus-infected cells to phosphorylate these nucleosides. Therefore, the selectivity of these nucleoside analogues must be based on their interaction with the reverse transcriptase, to which they have an affinity 100 times greater than their affinity for cellular DNA polymerase. This poor selectivity is responsible for many of the toxic effects of these drugs.

4.4.2. Glucosidase Inhibitors

Glucosidase inhibitors have been shown to reduce the infectivity of a number of viruses.[139] However, these compounds, including the carbohydrate analogues (Figure 4.4) deoxynojirimycin **(168)** and castanospermine **(169)**, have been most effective against HIV *in vitro*. They have been shown to alter the glycosylation of the HIV envelope glycoprotein (gp120), greatly reducing penetration of the virus into the cells. It has been suggested that a conformational change of the abnormal glycoprotein prevents cleavage of this protein, which is necessary for infection.[140]



(168)



(169)

Figure 4.4: The Structure of Some Alkaloid Antiviral Compounds

Since the initial discovery that castanospermine and DNJ are capable of reducing the infectivity of HIV, many analogues with increased activity and reduced toxicity have been prepared. The most effective compounds are *N*-alkyl analogues[141, 142]. *N*-Butyl DNJ has recently been introduced into clinical trials in the USA.

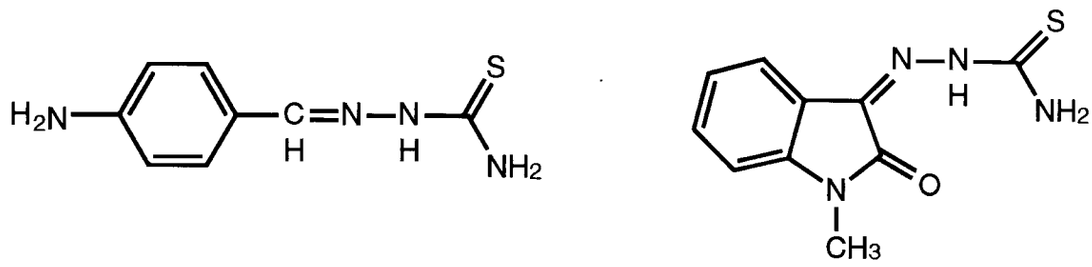
4.4.3. Metal Ion Chelators as Antiviral Agents

The presence of metal ions in both RNA and DNA polymerases has been well documented.[143] Zinc ions, in particular, appear to play an important role in the activity of nucleic acid polymerases.[144] The correlation between the concentration of zinc ions and the level of polymerase activity has been documented in several systems.[145-147] The presence of these metal ions suggests the possibility of inhibiting viral enzymes by the use of chelating agents to coordinate to essential metal ions. In the case of the influenza virus, a correlation has been found between the ability of pyrophosphate analogues to bind zinc and their *in vitro* antiviral activity.[148]

4.4.3.1. Thiosemicarbazones

Thiosemicarbazones (Figure 4.5) have been shown to be active against DNA and RNA viruses as well as tumours, protozoa and fungi. However, there is usually little margin between effective dose levels and toxicity. The

p-aminobenzaldehyde compound **(170)** was the first thiosemicarbazone reported to have antiviral activity.[149] Structure activity studies prompted by this compound led to 1-methylisatin β-thiosemicarbazone **(171)**, which when given orally, was successful in the prophylaxis of smallpox.[150]



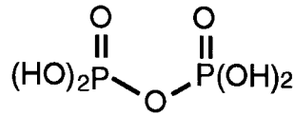
(170) **(171)**

Figure 4.5: Thiosemicarbazones with Antiviral Activity

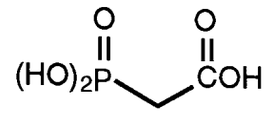
The inhibitory effects of isatin β-thiosemicarbazone **(171)** and its derivatives on vaccinia virus are produced late in the viral cycle. The mode of action of these compounds possibly involves metal ion chelation.[151] α-(*N*)-Heterocyclic thiosemicarbazones are known to inhibit the growth DNA viruses from the herpes family.[152] It is thought that this activity is occurs *via* a terdentate complex.[151]

4.4.3.2. Pyrophosphate Analogues

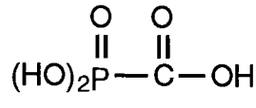
Analogues of inorganic pyrophosphate **(172)** such as phosphonoacetic acid (PAA) **(173)**, phosphonoformic acid (PFA) **(174)** (Figure 4.6) are known to inhibit the DNA polymerase of herpes simplex virus 1 (HSV-1) and the RNA transcriptase of influenza virus A. Methylene bisphosphonic acid **(175)**, although it is isosteric with inorganic pyrophosphate, has been found not to have this inhibitory activity. Interest in this class of compounds was initiated by the discovery that PAA **(173)** inhibited herpes viruses in animals.[153]



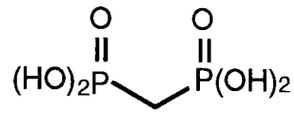
(172)



(173)



(174)



(175)

Figure 4.6: Pyrophosphate and Antiviral Pyrophosphate Analogues; Phosphonoformic Acid, Phosphonacetic Acid and Methylene Bisphosphonic Acid

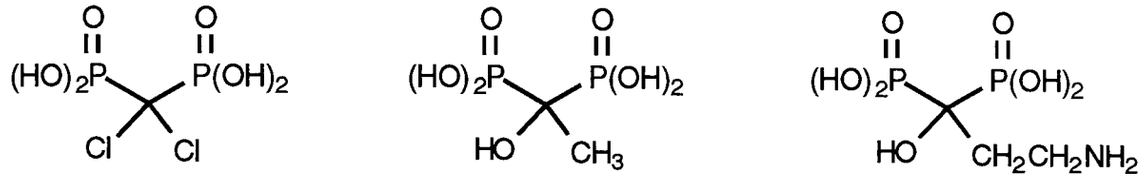
4.4. Mode of Action of Pyrophosphate Analogues

Data indicate that pyrophosphate analogues inhibit the herpes-induced DNA polymerases by acting on the enzymes without prior conversion to an active compound.[148] This activity appears to be related to the ability of these compounds to form stable chelates with a metal ion (probably zinc) at the active centres of the enzyme systems.[154] In the case of influenza virus, initiation of mRNA synthesis does occur in the presence of PFA **(174)**, but the elongation of the RNA chain does not occur. This indicates that PFA **(174)** inhibits the chain elongation of influenza virus mRNA during capping processes.[155]

4.5. Disadvantages of Pyrophosphate Analogues

PAA is known to accumulate in bones and teeth when given intravenously. In fact, the high affinity for bones and teeth of some bisphosphonic acids (Figure 4.7) for example, dichloromethylene-bisphosphonic acid (clodronate) **(176)**, 1-hydroxyethylidene-bisphosphonic acid (etidronate) **(177)** and 4-amino-1-hydroxybutylidene-bisphosphonic acid (alendronate) **(178)** for solid-phase calcium phosphate is used to therapeutic advantage.[156-158] These compounds have been shown to be useful in the

treatment of variety of osteolytic bone disorders including Paget's disease, hypercalcaemia of malignancy, osteolytic bone tumours and more recently osteoporosis.[159]



(176) **(177)** **(178)**

Figure 4.7: Clinically Used Bone Chelating Bisphosphonic Acids

Bisphosphonates are also commonly complexed with technetium-99 and used as bone imaging agents.[160] Although these bone-seeking properties of bisphosphonic acids are therapeutically useful for the treatment of bone disorders they are not desirable properties for antiviral agents.

A second major drawback is the inability of highly charged molecules such as PAA **(173)** and PFA **(174)** to penetrate the cell wall. Although PAA is a very potent inhibitor of viral DNA polymerase, concentrations of 200 μg/ml are required for activity *in vivo*. This is 100 times greater than is needed *in vitro*.

4.6. Structure-Activity Studies on Pyrophosphate Analogues

As can be seen, there are several opportunities for improving the efficacy of PAA and PFA *in vivo*. Extensive structure-activity studies have been carried out with a number of analogues of PAA and PFA against the herpes and influenza viruses.[161, 162] These demonstrate that there are strict structural requirements for antiviral activity.

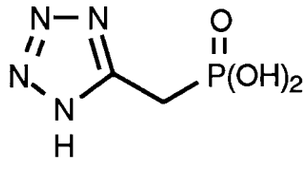
Esterification of either the carboxyl or the phosphoryl groups results in a marked reduction of antiviral activity *in vitro*. Blocking of the carboxylic

group with small alkyl esters such as methyl or ethyl only slightly decreased activity. However, larger esters resulted in a much greater loss of activity. The ionizability of the phosphono group appears to be much more important. Monophosphoryl esters retain some activity. However, the diethylphosphono ester is inactive, although, some activity is reported *in vivo*, probably due to hydrolysis of the ester in the cell liberating the free acid.[161]

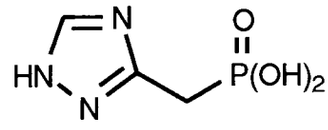
The phosphonic group is a very specific requirement for activity and can not be replaced by a sulfono, phosphinic or phosphine moiety. However, arsenoacetic acid showed strong inhibition of polymerase at high concentrations, but is inactive *in vivo*.

Replacement of the carboxyl group by a phosphoryl group gives rise to methylenebisphosphonic acid **(175)**. While the parent compound is devoid of activity, replacement of the methylene hydrogens by electron withdrawing groups leads to compounds which are good inhibitors of the RNA transcriptase of the influenza virus but have little or no anti-herpes activity.[162]

The use of the tetrazole moiety as an isostere for the carboxylic acid group is well accepted. A variety of heterocyclic analogues of PAA have been investigated (Figure 4.8). Both the tetrazole **(179)** and the triazole **(180)** analogues were found to have weak inhibitory activity against DNA polymerase induced by HSV-1. However, only the tetrazole compound **(179)** showed any activity against RNA transcriptase of influenza.[163]



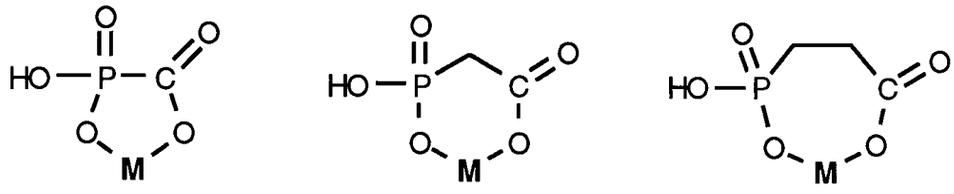
(179)



(180)

Figure 4.8: Tetazole and Triazole Analogues of Phosphonoacetic Acid

The distance between the phosphonic and the carboxylic group is extremely important. Only PAA **(173)**, and PFA **(174)** which is in general a more active antiviral agent than PAA **(173)**, show any antiviral activity. The homologue 3-phosphonopropionic acid has little antiviral activity. This is possibly due to the stability of the chelates that these compounds form with zinc (Figure 4.9). PFA forms a chelate with a five-membered ring **(181)** and PAA forms a chelate with six-membered ring **(182)**, whereas the propionic analogue forms a seven-membered ring chelate **(183)**. It is well known that the stability of cyclic metal chelates is 5>6>7.[164]



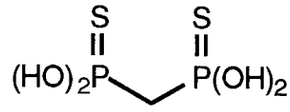
(181) **(182)** **(183)**

Figure 4.9: Metal Chelates of Phosphonoformic, Phosphonacetic, and Phosphonopropanoic Acids

Although methylenebisphosphonic acid **(175)** is a good isostere of pyrophosphoric acid, it shows little activity against the influenza or herpes viruses. It has been suggested that the isopolar properties of pyrophosphate analogues are as important as their isosteric properties.[165] This theory is supported by the fact that methylenebisphosphonic acids, in which the bridging carbon is substituted by an electron withdrawing substituent such as a halogen are active against the RNA polymerase of the influenza virus. Substituting the bridging carbon by an electron withdrawing group reduces the dissociation constant of the methylenebisphosphonic acid, making it isopolar with inorganic pyrophosphate ion in solution.

Thiophosphonoacetic acid **(184)** (Figure 4.10) exhibits greater activity than PAA against influenza[162] and appears to have a lower toxicity to cells.[166]

This increased activity is possibly related to the increased ability to bind zinc. The greater affinity of sulphur towards zinc, as predicted by Pearson rules for hard and soft acids and bases,[167] results in the thiophosphonate analogues forming stronger complexes with zinc than the fully oxygenated compounds.



(184)

Figure 4.10: Methylenebisthiophosphonic acid

4.6.1. Cycloalkane Pyrophosphate Analogues

Alkylation of the bridging carbon of PAA does not significantly reduce its antiviral activity.[161] The cyclopropyl analogue of PAA and methylenebisphosphonic acid have been synthesised and their activity against influenza virus assayed. The cyclopropyl PAA analogue retained most of the activity of the parent compound, while the methylenebisphosphonic acid analogue remained inactive.[168] This suggests the possibility that including the bridging carbon in an cycloalkane ring of greater than three carbons may result in compounds that, whilst retaining their antiviral activity, exhibit more desirable pharmacokinetic properties, such as increased cellular uptake and less deposition in bones.

The constraint of the P-C-C and the P-C-P bond angles by the cycloalkane ring may also significantly effect the ability of these compounds to chelate zinc and thus yield further structure-activity information. However, none of the other cycloalkane analogues (C4-C6) have been investigated.

4.7. Synthesis of Cycloalkane Bisphosphonic and Cycloalkane Phosphonoacetic Acid Analogues

Monoalkylations of tetraalkyl bisphosphonates and trialkyl carboxyphosphonates are well known. However, until recently, intramolecular alkylation to form cycloalkane compounds has proved more difficult than with the corresponding dialkyl malonate compounds. Early attempts at the monoalkylation of both the potassium[169] and sodium[170] salts of tetraethyl methylenebisphosphonate were reported to give low yields. The alkylation of the sodium salt of tetraisopropyl methylenebisphosphonate was reported to give a slightly improved yield.[171]

Later authors[172] reported low yields when the alkylation of tetraisopropyl methylene- and halogenomethylene-bisphosphonates was attempted using sodium, sodium hydride and butyllithium to form the active anions. However, these authors also reported that good yields of monoalkylated products were obtained when the thallium(I) salt of tetraisopropyl methylene- or halogenomethylenebisphosphonate was treated with an excess of alkyl iodide.

4.7.1. Synthesis of Cyclopropane Analogues

The syntheses of both cyclopropanebisphosphonic acid[173] **(191)** and 1-carboxycyclopropane-1-phosphonic acid[8] **(194)** have been reported.

4.7.1.1. Cyclopropanebisphosphonic Acid

Cyclopropanebisphosphonic acid **(191)** has been prepared *via* a multistep synthesis using the thallium(I) salt of tetraisopropyl methylenebisphosphonate **(195)** (Figure 4.11).[173] 3-Bis(di-*iso*-propylphosphono)-1-iodopropane **(190)** could not be prepared by the direct alkylation of the thallium(I) salt of tetraisopropyl methylenebisphosphonate in the presence of excess 1,2-diiodoethane. This necessitated the use of a stable

iodoalkane **(186)** with a substituent at the 2-position that could be converted into an iodo-substituent through a series of intermediate compounds **(187-189)**. Reaction with a second equivalent of thallium ethoxide and subsequent deprotection of the phosphonate esters afforded cyclopropanebispbosphonic acid **(191)**.

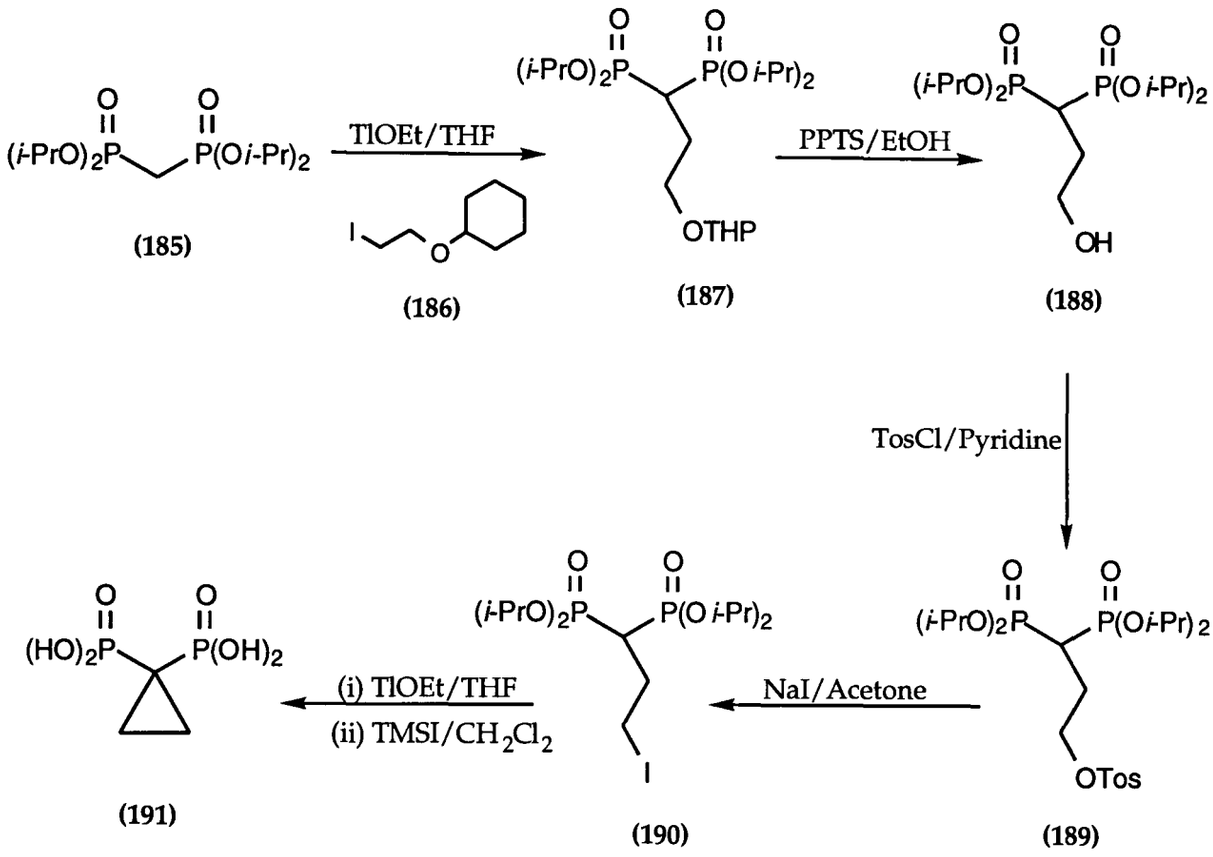


Figure 4.11: Synthesis of Cyclopropanebisphosphonic Acid

Attempts to use a similar strategy for the preparation of larger ring sizes led to problems. 4-Iodobutan-1-ol rapidly cyclised to form tetrahydrofuran, even in the dark at -20 ^{o}C. It was envisaged that this would be a problem for iodoalcohols containing three or more carbon atoms. The corresponding bromoalcochols could be prepared, but conversion of the bromine to iodine before alkylation of the tetraalkyl methylenebisphosphonate could take place would be necessary, as only iodoalkanes were found to react with the thallium salt.

4.7.1.2. Cyclopropane Phosphonoacetic Acid Analogue

The synthesis of diethyl 1-carbo-*t*-butoxycyclopropanephosphonic acid **(194)** (Figure 4.12) was carried out by phase transfer catalysed alkylation of *t*-butyl diethyl phosphonoacetate **(192)**.[8] This method is simple and high yielding and has been used in the synthesis of several 1-substituted-1-carboxycyclopropanes.[174] However, it was reported to be unsuccessful as a method for the preparation of dialkyl cyclopropanebisphosphonate[173]

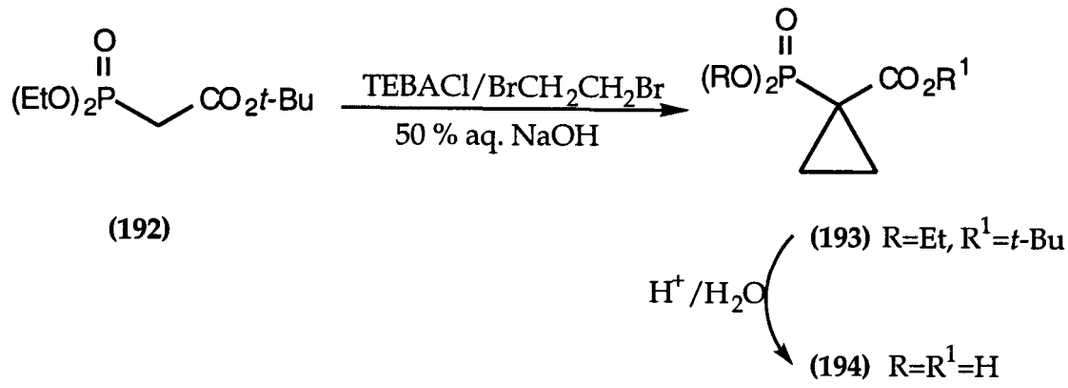


Figure 4.12: Synthesis of Diethyl 1-Carboxycyclopropanephosphonic Acid

4.8. Phase-transfer Catalysed Alkylations

The use of phase-transfer catalysis is well known as a method of alkylation and a variety of alkylations both intermolecular and intramolecular have been carried out.[175, 176] Compounds with a sufficiently acidic hydrogen can be conveniently alkylated by reaction with the desired alkyl halide in the presence of concentrated solution of sodium hydroxide and a suitable catalyst such as benzyltriethylammonium chloride. The main advantage of phase-transfer catalysed alkylations over more traditional methods using sodium hydride or butyl lithium is that there is no need to ensure that the reactions are carried out under anhydrous conditions.

The phase transfer method has also been described as extractive alkylation.[177] It is thought that the tetraalkylammonium halide **(195)** is converted to the tetraalkylammonium hydroxide salt **(196)** in the aqueous

layer which is which is taken up in to the organic phase. The ammonium hydroxide salt **(196)** is then able to extract the acidic hydrogen from the substrate **(197)** to form the reactive intermediate **(198)** which remains in the organic phase and reacts with the alkylhalide **(199)** to give the monoalkylated product **(200)** (Figure 4.13).[177] However, other authors have suggested that, as the catalysts employed are all essentially detergents, the reaction may occur either at the interface[178] or in the micellar phase.[179]

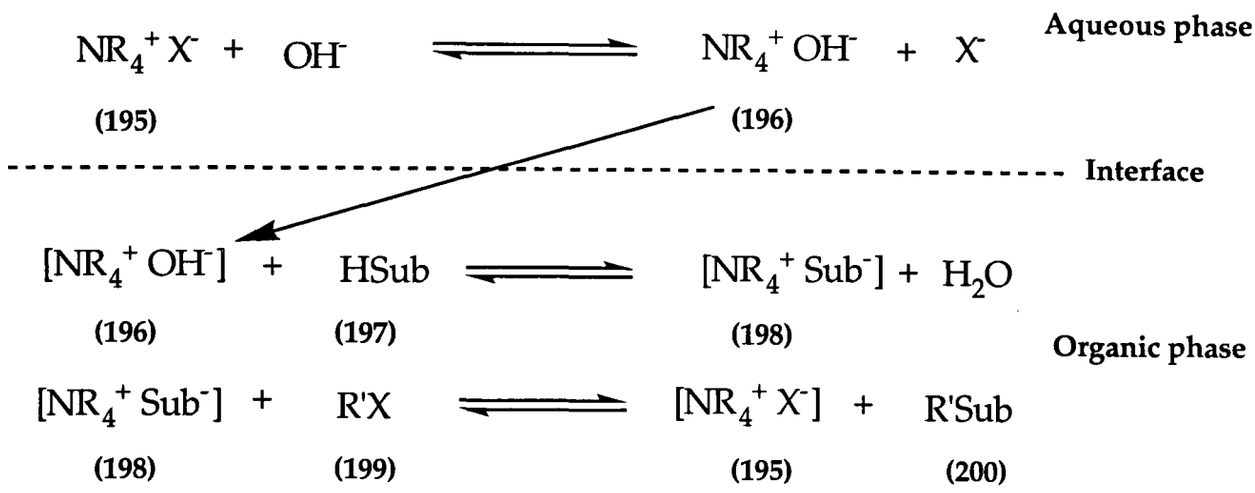


Figure 4.13: Suggested Mechanism for Extractive Alkylation

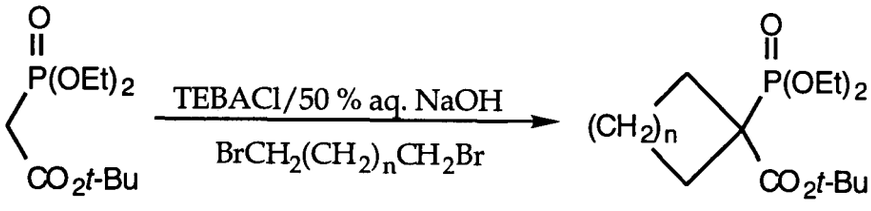
4.8.1. Phase-transfer Catalysed Synthesis of Tetraalkyl Cycloalkane-bisphosphonates and Trialkyl 1-Carboxycycloalkane-phosphonates

The simplicity of alkylation and intramolecular alkylation by phase-transfer catalysis and the complication of the multistep synthesis using thallium(I) anions, not to mention the hazards of working with thallium salts encouraged us to investigate the use of phase transfer catalysis as a general means of preparing a range of trialkyl 1-carboxycycloalkanephosphonates and tetraalkyl cycloalkanebisphosphonates.

4.9. Discussion

4.9.1. Synthesis of 1-Carboxycycloalkanephosphonic Acids

t-Butyl diethyl phosphonoacetate **(192)** was prepared in good yield by the Arbuzov reaction of triethyl phosphite with *t*-butyl bromoacetate.[8] Treatment of the resulting ester **(192)** with the required 1,ω-dibromoalkane (n=3-5), 50 % sodium hydroxide and benzyltriethylammonium chloride produced the desired cycloalkane compounds in moderate yields **(201-203)** (Scheme 4.1).



(192)

(201) n=1, 42 %
(202) n=2, 65 %
(203) n=3, 43%

Scheme 4.1.

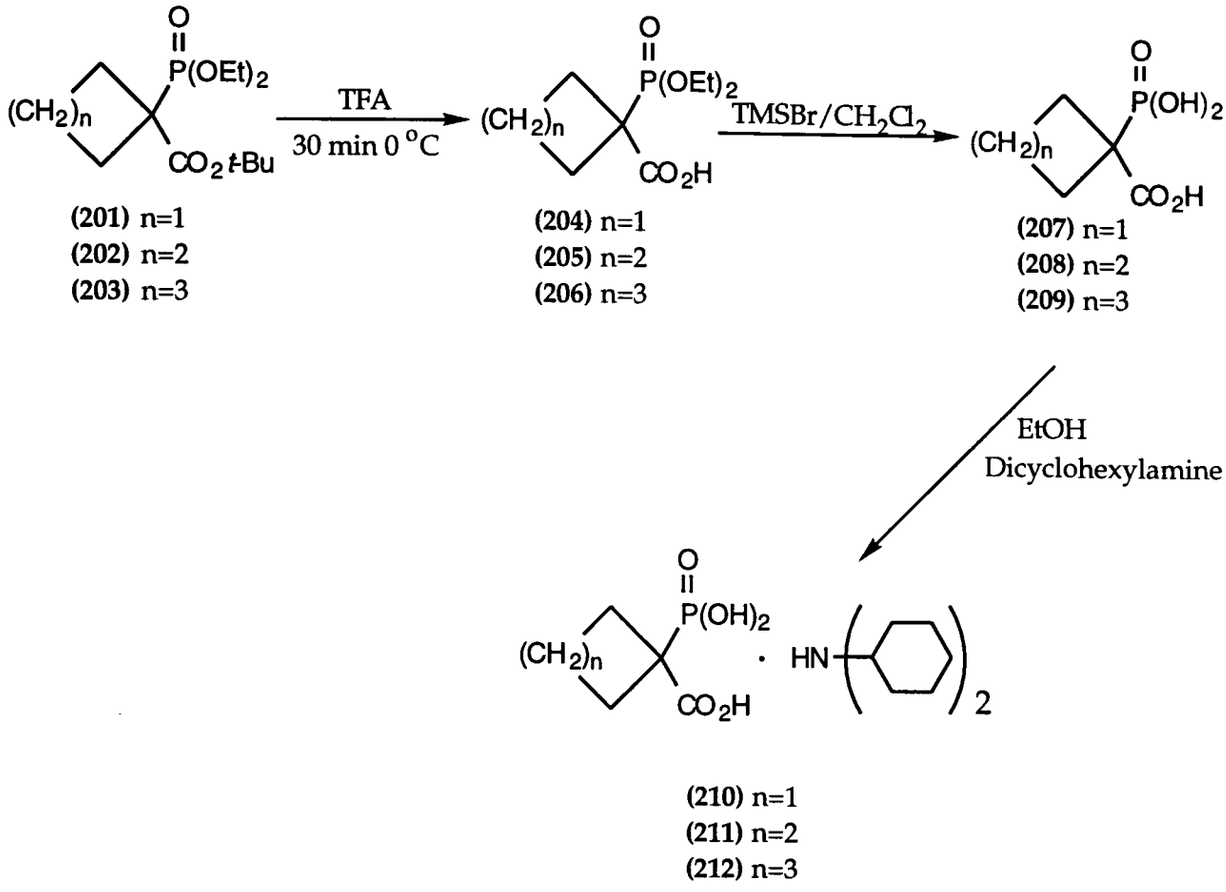
Reaction times for maximum yields ranged from 24-48 hours, depending on the ring size being formed. The cyclobutane and cyclopentane rings formed more rapidly than the cyclohexane ring. If the reaction of 1,5-dibromopentane and *t*-butyl diethyl phosphonoacetate **(192)** was stopped after only 24 hours, the monoalkylated product predominated. Presumably the initial alkylation occurs at a similar rate with all the alkyl halides, but the longer alkyl chain of the intermediate 6-(*t*-butylcarboxy)-6-(diethylphosphono)-1-bromohexane allows more freedom of movement to the alkyl chain, thus making the cyclisation more entropically disfavoured. Although the 1,ω-dibromoalkane was used as both reactant and solvent no evidence of alkylation by two molecules of the alkyl halide was seen. The excess dibromoalkane and unreacted tetraalkyl methylenebisphosphonate

were removed by Kugelrohr distillation. Final purification was carried out by chromatography on silica gel.

Hydrolysis of the *t*-butyl esters **(201-203)** (Scheme 4.2) was readily accomplished by treatment with trifluoroacetic acid at 0 °C.[8] Residual TFA was removed by washing a dichloromethane solution of the crude product in dichloromethane with brine. The diethyl 1-carboxycycloalkanephosphonates **(204-206)** were of sufficient purity to be used without further purification.

Dealkylation of the phosphonate ester groups was carried out with trimethylsilyl bromide.[172] Although dealkylation of the cyclopropane analogue using this method was reported to result in significant amounts (20 %) of side products arising from the opening of the cyclopropane ring,[173] in the case of the four, five and six membered rings the only product resulting from this reaction was the desired 1-carboxycycloalkanephosphonic acids **(204-206)**. The occurrence of side reactions in the deprotection of the cyclopropane compound is probably a reflection of the increased ring strain and different electronic character of the cyclopropane ring in comparison to the larger ring sizes.

The title compounds **(207-209)** were dissolved in ethanol and precipitated as their dicyclohexylamine salts **(210-212)**. Recrystallisation of the white powder yielded analytically pure samples of the target compounds.



(201) n=1
(202) n=2
(203) n=3

(204) n=1
(205) n=2
(206) n=3

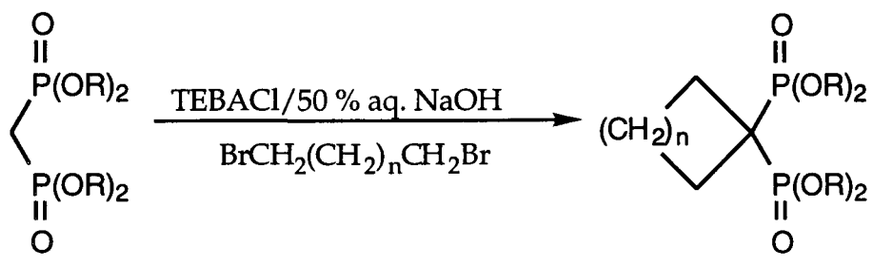
(207) n=1
(208) n=2
(209) n=3

(210) n=1
(211) n=2
(212) n=3

Scheme 4.2.

4.9.2. Synthesis of Cycloalkanebisphosphonic Acids

Treatment of tetraethyl methylenebisphosphonate or tetraisopropyl methylenebisphosphonate (Scheme 4.3) with the required 1,ω-dibromoalkane (n=3-5), 50 % sodium hydroxide and triethylbenzylammonium chloride and purification in a manner analogous to that described above produced the desired tetraalkyl cycloalkane-bisphosphonates **(214-216)** in moderate yields.



(213) R=Et
(185) R=*i*-Pr

(214) R=Et, n=1, 37 %
(215) R=*i*-Pr, n=2, 50 %
(216) R=*i*-Pr, n=3, 48 %

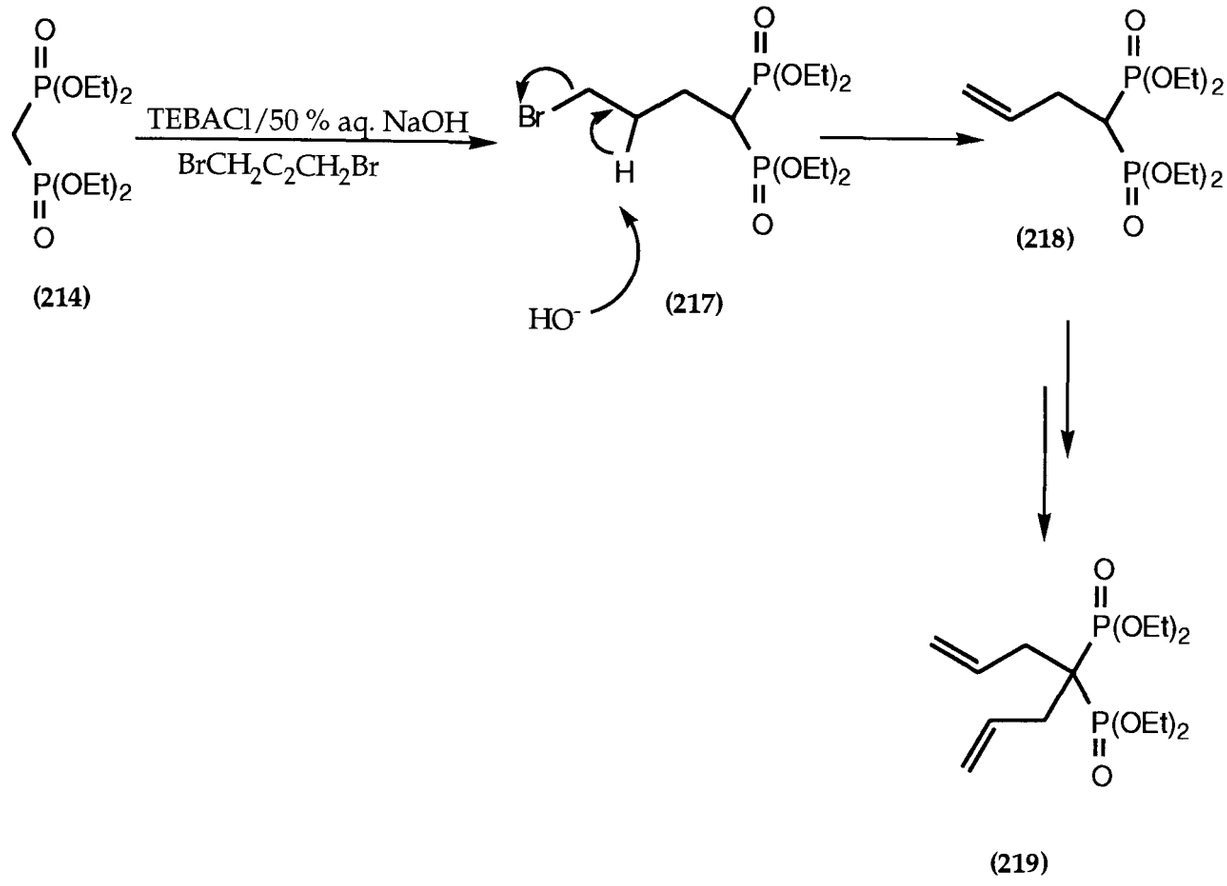
Scheme 4.3.

Although tetraethyl methylenebisphosphonate **(213)** was used as the substrate for the preparation of the cyclobutane compound **(214)**, use of the tetraethyl ester to prepare the corresponding cyclopentane compound resulted mainly in hydrolysis of the ester groups with only low yields (< 10 %) of diethyl cyclopentanebisphosphonate. Using the more hindered tetraisopropyl methylenebisphosphonate **(185)** led to much higher yields of the cyclopentane compound **(215)**. However, the use of tetraisopropyl methylenebisphosphonate **(185)** for the preparation of the cyclobutane analogue resulted in only monoalkylated compound. This may be due to the bulk of the four isopropyl groups and the bromine interacting in such a way that the intermediate can not adopt a conformation which is suitable for nucleophilic displacement of the bromine by the carbanionic centre.

The considerably longer reaction times of all these reactions compared to those of the malonate analogues[8, 174] is possibly due to the increased bulk of the phosphonates compared to the carboxylates. Reaction times for the malonates are of the order of one hour compared to one to two days for the corresponding phosphonates. A second factor that could account for the increased reaction time is that the phosphonates are more electron wtihdrawing than malonates, thus the anions of the bisphosphonates will be more stable and hence less reactive, than the anions of malonates.

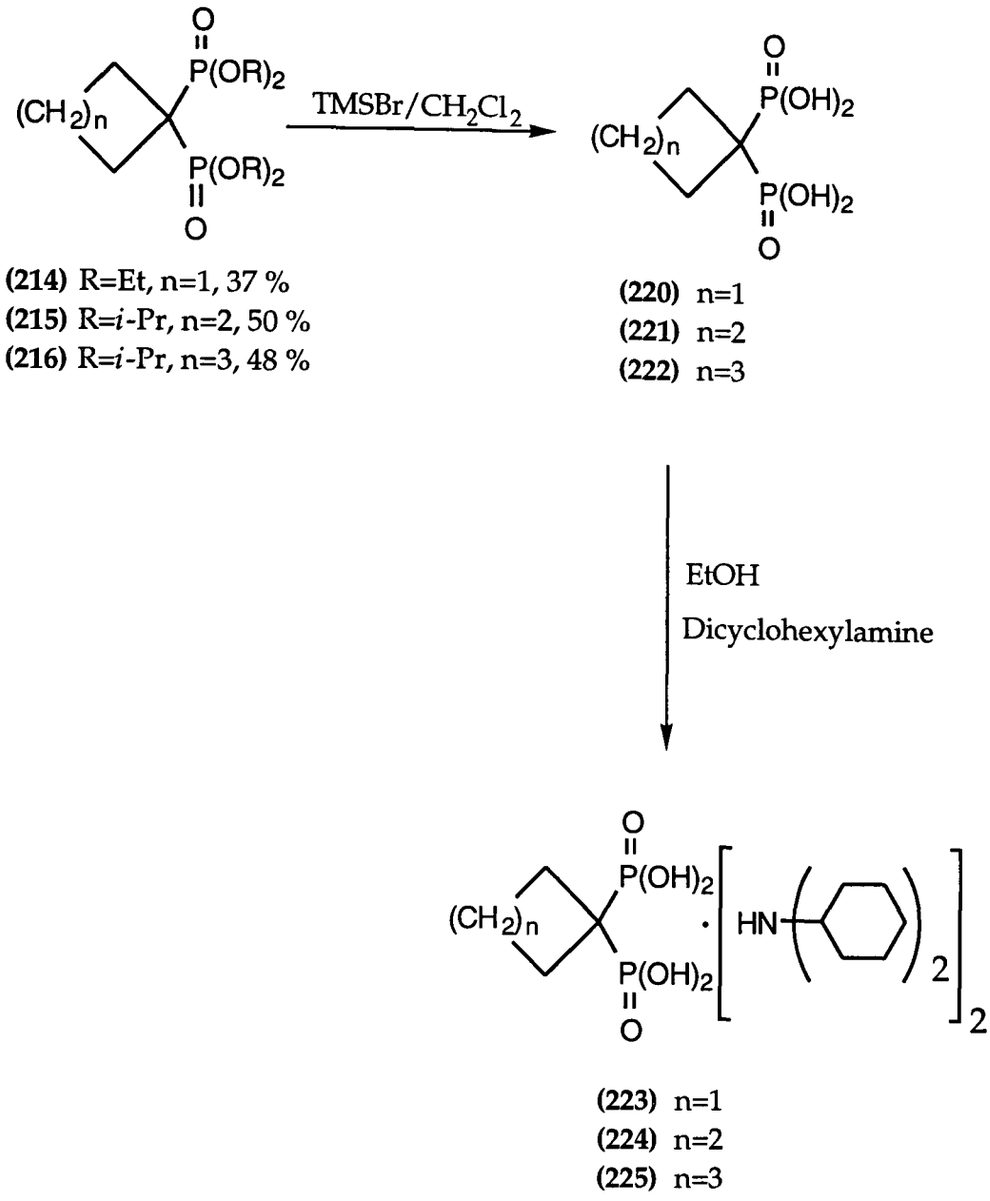
It is interesting that, of the six compounds produced by this method, only in the case of the reaction between tetraethyl methylenebisphosphonate and 1,3-dibromopropane to form tetraethyl cyclobutanebisphosphonate **(213)** was there any evidence of by-product **(219)** resulting from alkylation by a second molecule of the alkylbromide (Scheme 4.4). In this case elimination of HBr also occurred to form tetraethyl diprop-2-enemethylenebisphosphonate **(219)**, which occurred in yields of less than 10 %. The fact that only monoalkylation occurs when the tetraisopropyl ester is used as a substrate indicates that there is also considerable strain on the tetraethyl intermediate to

adopt a conformation favourable to intramolecular displacement of bromide. The first elimination of HBr most likely occurs from the intermediate compound **(217)** before the intermolecular alkylation of **(218)** by the second molecule alkyhalide, thus both reducing steric hindrance and preventing intramolecular alkylation.



Scheme 4.4.

All the cycloalkane rings were found to be stable under the conditions of dealkylation of the phosphonate ester groups, which was mediated with trimethylsilyl bromide as described above.[172] The crude bisphosphonic acids **(220-222)** (Scheme 4.5) were obtained as viscous oils, treatment of which with dicyclohexylamine and ethanol, in a manner identical to that described for the 1-carboxycycloalkanephosphonic acids, yielded analytically pure samples of the title compounds as bisdicyclohexylamine salts **(223-225)**.



(214) R=Et, n=1, 37 %
(215) R=*i*-Pr, n=2, 50 %
(216) R=*i*-Pr, n=3, 48 %

(220) n=1
(221) n=2
(222) n=3

(223) n=1
(224) n=2
(225) n=3

Scheme 4.5.

Despite earlier reports of the unreactivity of the anions of tetraalkyl methylenebisphosphonates prepared by conventional means,[169-172] during the course of the work described above, two papers reporting the preparation of various 1-substituted-cycloalkanephosphonates appeared in the literature.[9, 180]

Tetraethyl cyclopentane- **(228)** and cyclohexanebisphosphonates **(229)**, as well as diethyl 1-cyanocyclohexane- **(230)** and diethyl 1-carboethoxycyclohexanephosphonates **(231)** (Figure 4.14), were prepared in 30-50 % yield by the reaction of the required substituted methylenephosphonate with an excess of sodium hydride and dibromoalkane in THF.[180]

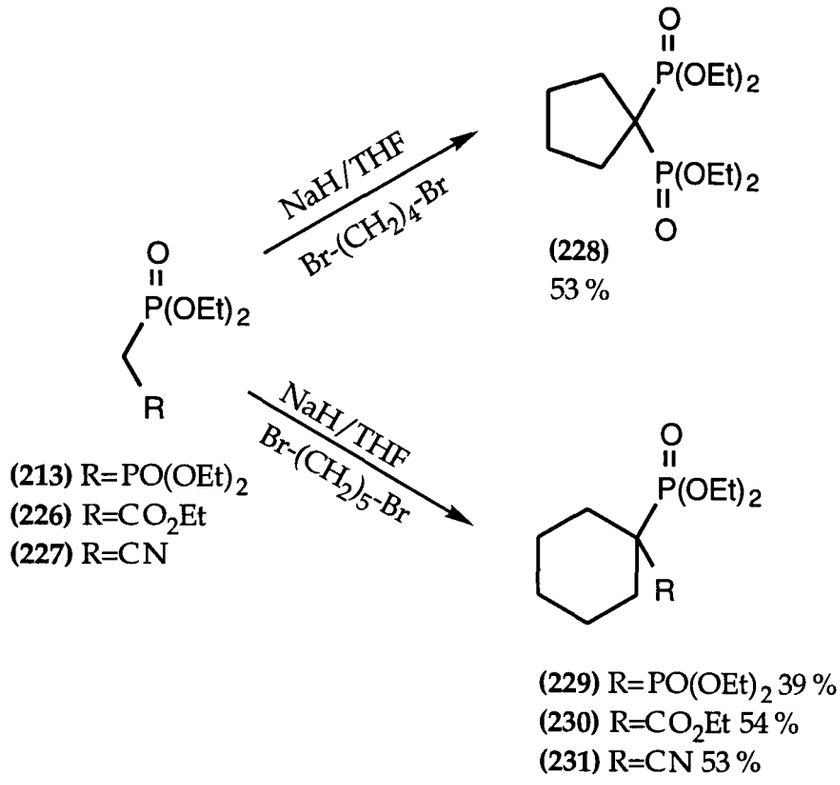


Figure 4.14: Synthesis of 1-Substitutedcycloalkanephosphonates

Reaction of tetrakis(bromomethyl)benzene or 2,2'-bis(bromomethyl) biphenyl with tetraethyl methylenebisphosphonate or triethyl phosphonoacetate and sodium hydride affords aromatic bisphosphonates and carboxyphosphonates **(232-234)** (Figure 4.15) in moderate yield.[180]

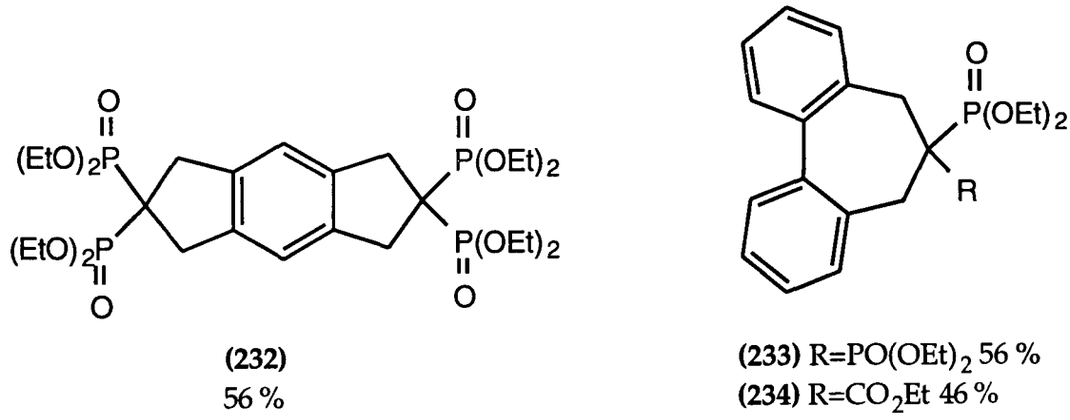
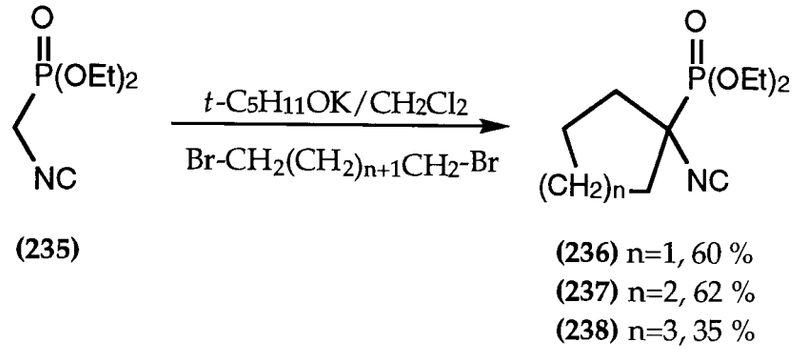


Figure 4.15: Aromatic 1-Substituedcycloalkanephosphonates

Diethyl 1-isocyanocycloalkanephosphonates **(236-238)** (Figure 4.16) were prepared by the reaction of two equivalents of potassium *t*-pentoxide and the required dibromoalkane with diethyl isocyanomethylphosphonate **(235)** in dichloromethane at -70 ^{o}C in yields of 35-60 %.[9]



(235)

(236) n=1, 60 %
(237) n=2, 62 %
(238) n=3, 35 %

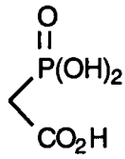
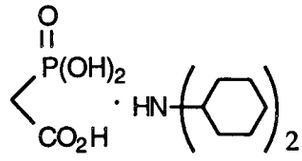
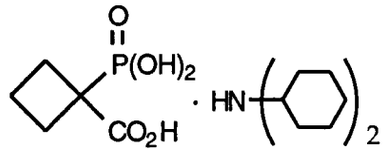
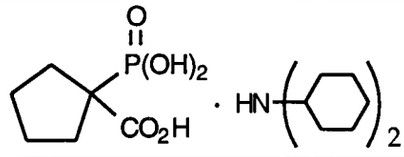
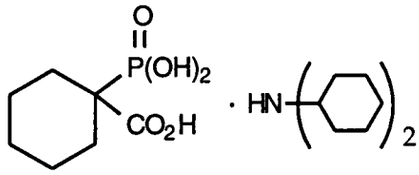
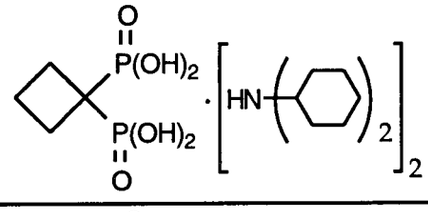
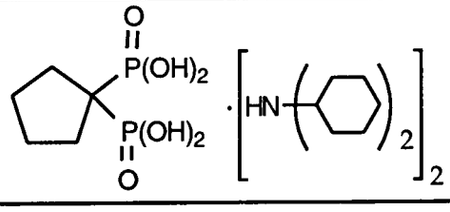
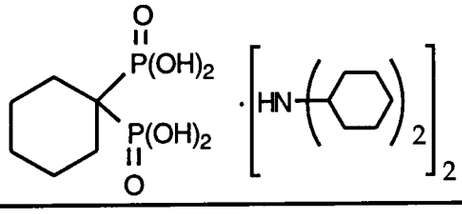
Figure 4.16: Synthesis of Diethyl 1-Isocyanocycloalkanephosphonates

In light of the earlier reports that indicated the difficulty of alkylating sodium and potassium salts of substituted methyl phosphonates,[169, 170, 172] it can only be assumed that the low yields were due to side reactions caused by impurities in the starting materials.

4.10. Antiviral Activity of 1-Carboxycycloalkane phosphonic Acids and Cycloalkanebisphosphonic Acids

The inhibitory effect of our PAA analogues upon (HSV-1) replication was analyzed using the plaque reduction assay as described by Mao *et al.*[161] The assay was performed in triplicate, using 100μg of compound per cm^3. Inhibition of virus replication was determined by comparing the number of herpes virus-induced plaques in the presence and absence of the compound. The results of these assays are shown in table 4.2 below.

Table 4.2: Antiviral Activity of Cycloalkane Compounds

Compound	% Inhibition of PFU
	99.5[161]
	99.5[161]
	< 1
	< 1
	8.5
	< 1
	< 1
	< 1

4.11. Conclusion

We have shown that phase transfer catalysed alkylation is an acceptable method of preparing cycloalkane 1-substitued-1-phosphonate compounds.[181] Although alternative methods have been proposed for the inter- and intramolecular alkylation of 1-substituted-1-methylenephosphonates, we believe our method to be superior as it does not require anhydrous conditions. Furthermore, the phase transfer catalysed reaction is the only reported route to 1-substituted cyclobutane-1-phosphonates.

Of the cycloalkane PAA analogues tested, only the cyclohexane compound showed significant activity as an inhibitor of HSV-1 activity, being 10-100 times less active than PAA. None of the other PAA analogues, nor the alicylic methylene bisphosphonic acids showed activity against HSV-1. We propose that, due to the greater flexibility of the cyclohexane ring in comparison to the smaller ring compounds, the P-C-C bond angle of the cyclohexyl compound is closer to that of PAA than the P-C-C bond angle of the cyclobutane or the cyclopentane compounds. Although the compounds were essentially inactive against HSV-1, it is interesting to note that they were less toxic toward the host cells than PAA in all cases.

Chapter 5

α-Phosphoryl Sulfoxides and Related Compounds as Potential Asymmetric Catalysts

5.1. Introduction

The property of chirality often determines the behaviour of molecules in many ways. It is responsible for the ability of a compound to interact with other chiral compounds at a molecular level. This in turn determines a number of characteristics of a compound, for example its taste, its smell and its medicinal activity. As chemicals, both natural and synthetic, find wide use in our everyday life, from medicines and food additives to pesticides and perfumes, it is understandable that for the production of these compounds it is preferable to secure them in an optically active form.[182]

Since the thalidomide tragedy of the late 1950s, where one enantiomer of the drug was a harmless sedative and the other a potential teratogen, various drug approval agencies are now increasing their requirements for the approval and registration of drugs capable of showing optical isomerism. In the worst case, e.g. Thalidomide, the opposite antipode of a compound with desirable activity can cause severe side-effects. Even in the best case scenario, where the opposite enantiomer is simply devoid of any activity, it means that 50 % of the dose of a drug is inactive. Thus, the stereoselective synthesis of compounds remains one of the greatest challenges facing synthetic chemists.

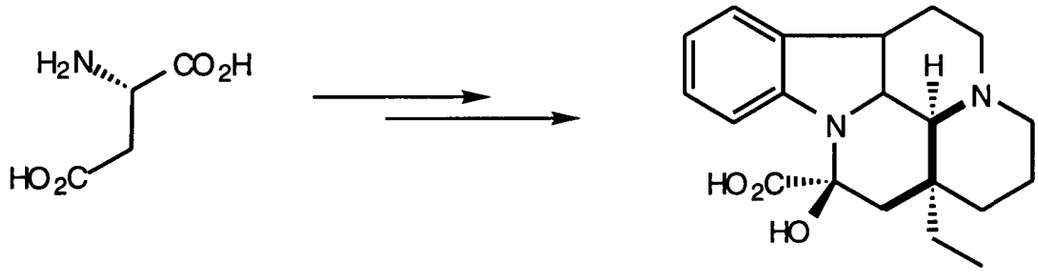
5.1.1. Methods for the Preparation of Enantiomerically Pure Compounds

One of the oldest methods for the preparation of enantiomerically pure compounds involves resolution of the enantiomers. The target compound is prepared as a racemic mixture and then the isomers are separated, usually *via* a diastereomeric salt derivative. The major disadvantage of this method is

that a maximum of 50 % yield can be obtained and unless the unwanted isomer can be epimerised, it often ends up as waste. Despite this, crystallisation of diastereomeric derivatives is common practice, even on an industrial scale.[182]

A more economic approach is to design a synthetic route involving an asymmetric transformation to deliver the desired chirality. There are now a number of methods available to the organic chemist for asymmetric synthesis of chiral compounds. Asymmetric synthesis can be defined as any synthetic operation that produces a new chiral centre in an enantiomerically enriched form.

The use of chiral starting materials from the chiral pool provides a valuable method of controlling the stereochemistry of subsequent reactions and thus the overall stereochemistry of the product. The synthesis of (+)-vincamine **(239)** (Figure 5.1) utilised the chiral centre of L-aspartic acid **(29)** as the sole source of chiral information in the construction of the three chiral centres of the target compound.[183]



(29) **(239)**

Figure 5.1: Synthesis of (+)-Vincamine from L-Aspartic Acid

Another possibility is to introduce a chiral centre in to a molecule as a chiral auxiliary. The express purpose of this initial chiral centre is to control the stereochemistry of subsequent reaction(s). The chiral originator is removed from the molecule when its stereodirecting effect is no longer needed. The

inherent drawback of this technique is that two extra synthetic steps are required: one to introduce the chiral auxiliary and one to remove it. In some cases another disadvantage is the loss of the chiral auxiliary, although non-destructive methods for the removal of chiral auxiliaries are becoming popular. The classic example of this method of asymmetric synthesis is the use of Evans' chiral oxazolidone auxiliaries (Figure 5.2).[184]

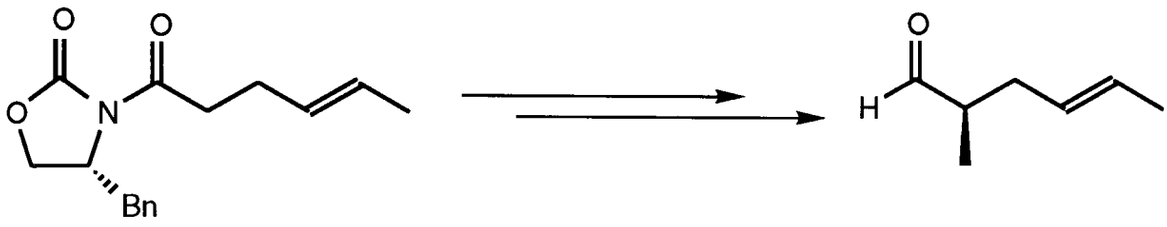


Figure 5.2: Evans Chiral Oxazolidone Auxiliary

The final group of asymmetric reactions involves processes where the chiral information is brought transiently in to the reaction system, usually through the transition state. These processes are catalytic with respect to the chiral moiety.[182] External asymmetric inductions are economically the most desirable, since only a catalytic amount of the chiral originator is required and this can later be recovered in its original form. One of the most intriguing and synthetically valuable examples of a catalytic enantioselective reaction involve the addition of organometallic reagents to carbonyl compounds.[185]

5.2. Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds

The organometallic alkylation of aldehydes or ketones is a simple and common synthetic operation. The development of a chiral version of this reaction, leading to optically active alcohols is obviously desirable because of its high synthetic utility. Enantioselective addition of organometallic reagents to aldehydes affords optically active secondary alcohols, which are

components of many naturally occurring compounds, biologically active compounds and materials such as liquid crystals.

The two main methods for the enantioselective synthesis of optically active secondary alcohols are the enantioselective alkylation of aldehydes and the enantioselective reduction of ketones. The former reaction can achieve formation of optically active alcohols with concurrent carbon-carbon bond formation. Despite the advantage of this reaction, the enantioselective addition of organometallic reagents to aldehydes had, until recently, only been achieved with low to moderate enantioselectivities.[186]

A non-racemic chiral environment can be introduced to organometallic compounds by (1) co-ordination of an aprotic chiral complexing agent or solvent to the metallic centre or (2) modification of organometallics by protic auxiliaries such as optically active hydroxy or amino compounds, giving organometallic alkoxides or amides, respectively. Several highly enantioselective additions to prochiral aldehydes have now been reported. For example, optical yields of >90% were reported by the use of a chiral 1,2-diamine/alkylithium, diamino alcohol/alkylithium, β-sulfononamido alcohol/alkyltitanium combined system or Li/Mg binary organometallic agents modified by optically active 2,2′-dihydroxy-1,1′-binapthol. However, in most of these reactions, stoichiometric or even excess amounts of chiral reagent to organometallic reagent or carbonyl substrate are required. This limits the economic and practical usefulness of these reactions.[185]

5.2.1. Desirable Characteristics for Asymmetric Catalysts of Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds

In order to obtain a high degree of enantioselectivity, the chiral anionic ligand must possess a suitable 3-dimensional structure which clearly

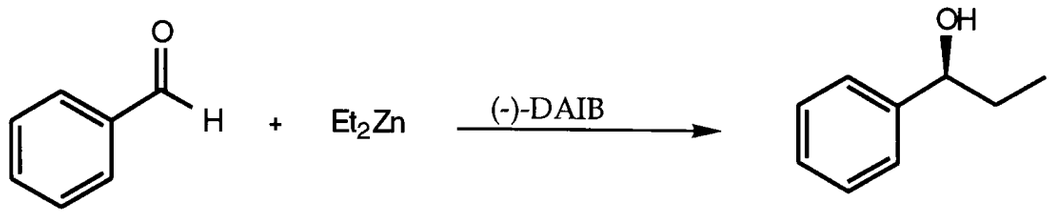
differentiates between the diastereomeric transition states of the alkyl delivery step. In addition to this the rate of alkylation of the chirally modified organometallic should substantially exceed that of the original achiral reagent and the chiral ligand must be readily detached from the initially formed metal alkoxide by the action of the alkyl donor or carbonyl substrate to establish the catalytic cycle.[185]

Of the various available organometallic compounds, dialkylzinc acts as an ideal alkyl donor for catalytic asymmetric alkylation. In most solvents dialkylzinc compounds do not react with aldehydes, forming instead a reversible donor-acceptor complex. Even at elevated temperatures alkylation takes place only very slowly.[185] However, it is know well known that in the presence of certain asymmetric catalysts, e.g. β-amino alcohols, this reaction proceeds rapidly and in many cases with high enantioselectivity.

5.3. Enantioselective Addition of Organozinc Reagents to Aldehydes

Until recently the addition of dialkylzincs to aldehydes was rarely utilised in organic synthesis, because the reaction is extremely sluggish and because side-reactions such as reduction usually occur. The clean nucleophilic addition of diethylzinc to benzaldehyde in the presence of a β-amino alcohol derived from (*S*)-proline, was first reported by Mukaiyama. The β-amino alcohol accelerates the carbon-carbon bond forming reaction to afford 1-phenyl-propanol in 76 % yield.[187] Although no asymmetric induction was observed in this reaction, the formation of a carbon-carbon bond from a dialkylzinc and an aldehyde suggested the possibility of asymmetric induction using an appropriate β-amino alcohol. Oguni and Omi used (*S*)-leucinol as a chiral catalyst and obtained optically active 1-phenyl-propanol **(241)** from benzaldehyde **(240)** with moderate optical purity (49 % ee).[188] Two years later Noyori and co-workers realised the first highly enantioselective alkylation of

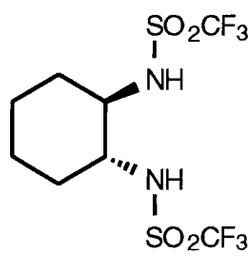
aldehydes by diethylzinc, catalysed by (-)-3-*exo*-(dimethylamino)isoborneol ((-)-DAIB) **(244)** leading to a 1-phenylpropanol **(241)** in up to 99 % ee (Figure 5.3).[189]



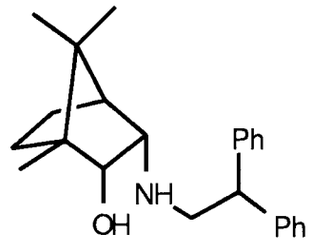
(240) **(241)**
99 % ee

Figure 5.3: Asymmetric Catalysis by (-)-DAIB

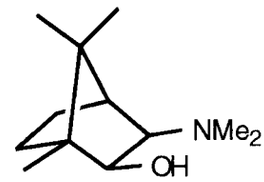
Since the work of Noyori a number of bidentate protic auxiliaries and aprotic ligands have been screened, and this enantioselective alkylation has been extended to a range of alkylating agents and aldehyde substrates. Homogenous chiral catalysts that have been utilised include amino alcohols, piperazines, transition metal salts with diols, quarternary ammonium salts, diols and oxazaborolidines, some examples of highly enantioselective co-catalysts are given below **(242-247)** (Figure 5.4).[189]



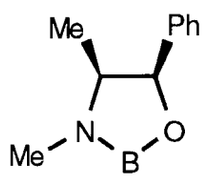
(242)



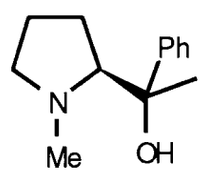
(243)



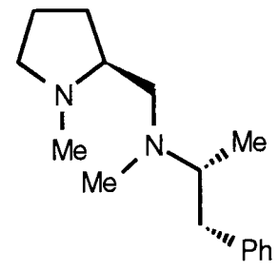
(244)



(245)



(246)



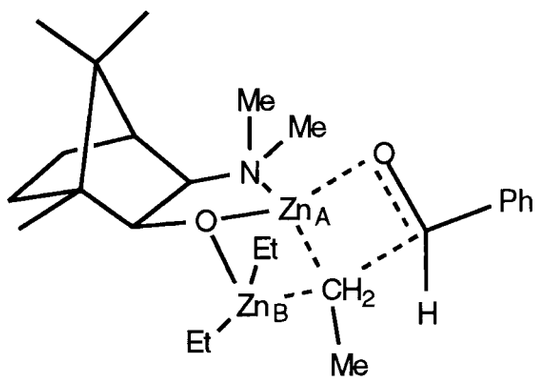
(247)

Figure 5.4: Highly Enantioselective Asymmetric Catalysts for the Addition of Dialkylzincs to Aldehydes

5.3.1. Mechanism of Addition of Dialkylzinc to Aldehydes

The catalysis of this reaction by compounds such as β-amino alcohols may be explained as follows. Monomeric dialkylzincs have a sp-hybridised linear geometry with approximately 1.95 Å bond length between the zinc and the carbon atoms and are inert to carbonyl compounds because the alkyl-metal bond is relatively non-polar. Dimethyl zinc is known to form a complex with 1,3,5-trimethylhexahydro-1,3,5-triazine. X-ray analysis revealed that the co-ordination chemistry of the zinc atom changes to become tetrahedral with a 145° carbon-zinc-carbon bond angle and the bond length between the zinc and the carbon atoms increases (1.98 Å). The overall result of this is an increase in the energy of the zinc-carbon bond and an increase in the nucleophilicity of the methyl group of the dimethyl zinc.[189]

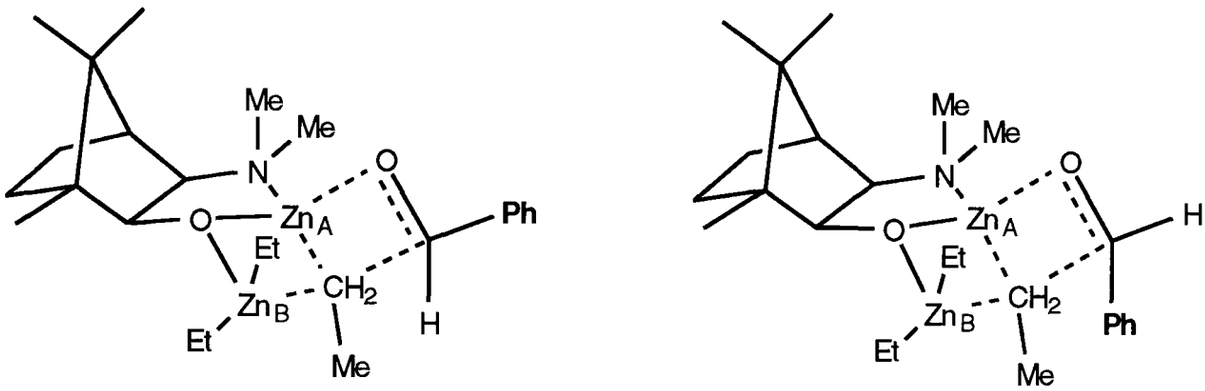
The exact mechanism of the alkyl transfer reaction remains to be elucidated. However, the enantioselective alkylation is thought to proceed *via* a series of dinuclear complexes. Three possible transition state complexes have been postulated.[185] The folded bicyclic transition state **(248)** as illustrated by the diastereomeric structure (Figure 5.5) is the most favoured. This mixed ligand dinuclear complex, in going from the ground state to the transition state increases both the electrophilicity of the aldehyde and nucleophilicity of the alkyl group as is necessary for this reaction.



(248a)

Figure 5.5: Proposed Transition State Complex for the Reaction Between Diethylzinc andBenzaldehyde in the Presence of (-)-DAIB

In the case of the catalyst DAIB, the more Lewis acidic DAIB-chelated $Zn_{(A)}$ accommodates the aldehyde substrate, increasing the electrophilicity at the carbon atom, and the bridging alkyl rather than the terminal alkyls act as the migrating group **(248a)**. Although the electron density of the bridging alkyl in the ground state is slightly lower than that of the terminal alkyl, the $Zn\text{-}R_{bridging}$ bond is more polarisable than the $Zn\text{-}R_{terminal}$ linkage.[185] The stereochemical bias is thought to be provided by non-bonded repulsion of the carbonyl substituents from the terminal alkyl group attached to Zn_B. In this case (Figure 5.6), the *S*-geometry **(248a)** is obviously favourable over the *R*-generating transition state **(248b)**.[189] The alkyl group is then added to the *Si* face of the aldehyde to afford a chiral alkyl zinc alkoxide.[186]



(248a)
S-generating

(248b)
R-generating

Figure 5.6: Stereocontrol of the Reaction Between Diethylzinc and Benzaldehyde

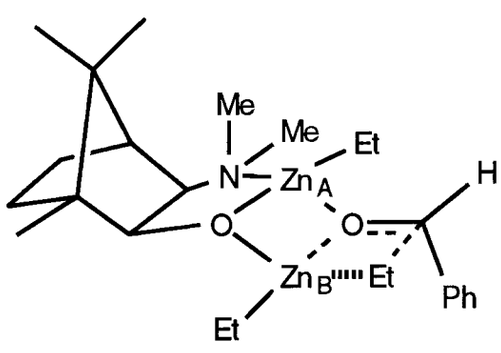
The sense of asymmetric induction may be conceived as controlled by the chirality of the 5/4-fused bicyclic structures. The (*S*)-configured zinc alkoxide is derived from the enantiomer having (*S*)-Zn and (*S*)-O configurations (Figure 5.6), while the (*R*)-alkoxide is derived from the (*R*)-Zn and the (*R*)-O enantiomer. Configurations of the catalyst of α-*S* or β-*R* has been reported to give preference to formation of the (*S*)-enantiomer whilst the (*R*)-enantiomer is stabilised by α-*R* or β-*S* configurations.

A good correlation is observed between reactivity and enantioselectivity. Higher enantioface selection is generally obtained along

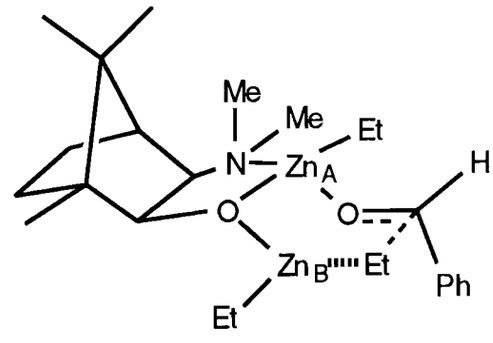
with faster reactions. The degree of enantioselectivity depends primarily on the bulkiness of the substituents at the α-carbon. Direct interaction between the carbonyl substituents and the α- or the β-substituents of β-amino alcohols is unimportant.[185]

Reaction of benzaldehyde **(240)** and diethylzinc does not occur at 0 °C in the abscence of a catalyst (e.g. DAIB) and, notably, no alkylation occurs when equimolar amounts of catalyst and diethylzinc are present. This indicates that a complex formed from a 1:1 ratio of catalyst and diethylzinc can not alkylate benzaldehyde despite the presence of an alkyl-zinc bond, suggesting that two zinc atoms per aldehyde are responsible for the alkyl transfer reaction.[185]

The bicyclic transition state **(249)** (Figure 5.7) could give an alternative explanation for the stoichiometry and stereochemistry of the organozinc reaction. Such a mechanism involving the transfer of a terminally located alkyl group to the electrophilically activated, bridged carbonyl carbon has also been suggested for the reaction of trimethylalluminium and benzophenone. A third possibility is the monocyclic six-centred transition state **(250)**, analogous to that proposed for the reaction of trimethylaluminium and propiophenone, which is also in accordance with experimental findings.[185]



(249)



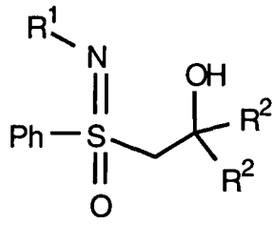
(250)

Figure 5.7: Alternative Transition State Complexes for the Reaction Between Diethylzinc and Benzaldehyde in the Presence of (-)-DAIB

5.3.2. Recent Developments in the Search for Asymmetric Catalysts for the Addition of Dialkylzincs to Aldehydes

Most of the known asymmetric catalysts for the addition of dialkylzinc to aldehydes are from three main classes: β-amino alcohols, diamines and diols.[185, 186] More recently, it has been found that a wider range of compounds can catalyse, enantioselectively, this type of reaction.

β-Hydroxy sulfoximides **(251)** (Figure 5.8) are reported to accelerate the addition of diethylzinc to aldehydes with high enantiocontrol.[190] The asymmetric induction was found to be highly dependent on the structure of the catalyst. The best selectivities were found with compounds having two alkyl substituents at the hydroxy bearing β-carbon. In the absence of an aldehyde, a dimeric zinc alkoxide complex was found to form between the β-hydroxy sulfoximide and the diethylzinc. In this dinuclear zinc complex two zinc alkoxides are bridged *via* their zinc and oxygen atoms to form a four-membered Zn_2O_2 heterocycle.[190] Similar complexes have been reported for other known catalysts, suggesting that the catalytic mechanism of this compound is similar to that reported for those catalysts.



(251)

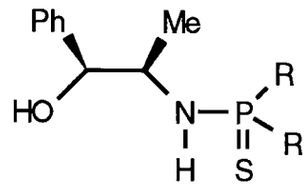
R^1= Me, Et, Tos, TBS

R^2=$(CH_2)_3$, $(CH_2)_9$, Me

Figure 5.8: β-Hydroxy Sulfoximides

Chiral dialkyl thiophosphoramidates **(252)** (Figure 5.9) derived from norephedrine have been shown to be highly enantioselective catalysts for the addition of dialkylzincs to aldehydes. Treatment of benzaldehyde **(240)** with a

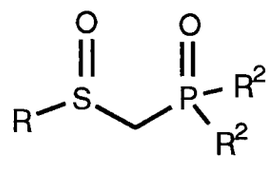
diethylzinc in the presence of titanium *iso*-propoxide and a dialkyl thiophosphoramidate **(252)** afforded 1-phenyl-propanol **(241)** in high yield and enantioselectivity (74-97 % ee).[191]



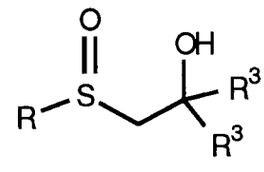
(252)
R=OMe, OEt, Me

Figure 5.9: Dialkyl thiophosphoramidate

These findings encouraged us to investigate the role of other types of compounds as potential catalysts for the addition of dialkylzinc to aldehydes. In particular, we were interested in examining the activities of substituted chiral sulfoxides (Figure 5.10) such as α-phosphoryl sulfoxides **(253)** and β-hydroxy sulfoxides **(254)**. Although both these types compounds have played significant roles in asymmetric synthesis, as yet no investigation of these compounds as asymmetric catalysts by exploiting their ability to complex metal ions has been undertaken.



(253)



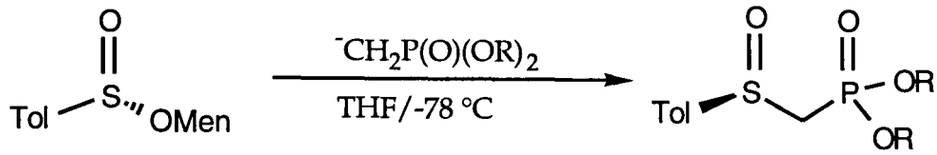
(254)

Figure 5.10: α-Phosphoryl Sulfoxides and β-Hydroxy Sulfoxides

5.4. Discussion

5.4.1. Synthesis of α-Phosphoryl Sulfoxides

Enantiopure dialkyl phosphorylmethyl *p*-tolyl sulfoxides (Scheme 5.1) are easily prepared by reaction of α-lithio diethyl methanephosphonate with the commercially available, desired diastereoisomer of menthyl *p*-toluenesufinate **(255)**.[192] The reaction proceeds with inversion of stereochemistry at the sulfoxide centre. Using this one step synthesis (Scheme 5.1), (*R*)-diethyl phosphorylmethyl *p*-tolyl sulfoxide **(256)** and (+)-(*R*)-di-*iso*-propyl phosphorylmethyl *p*-tolyl sulfoxide **(257)** were prepared.



(255)

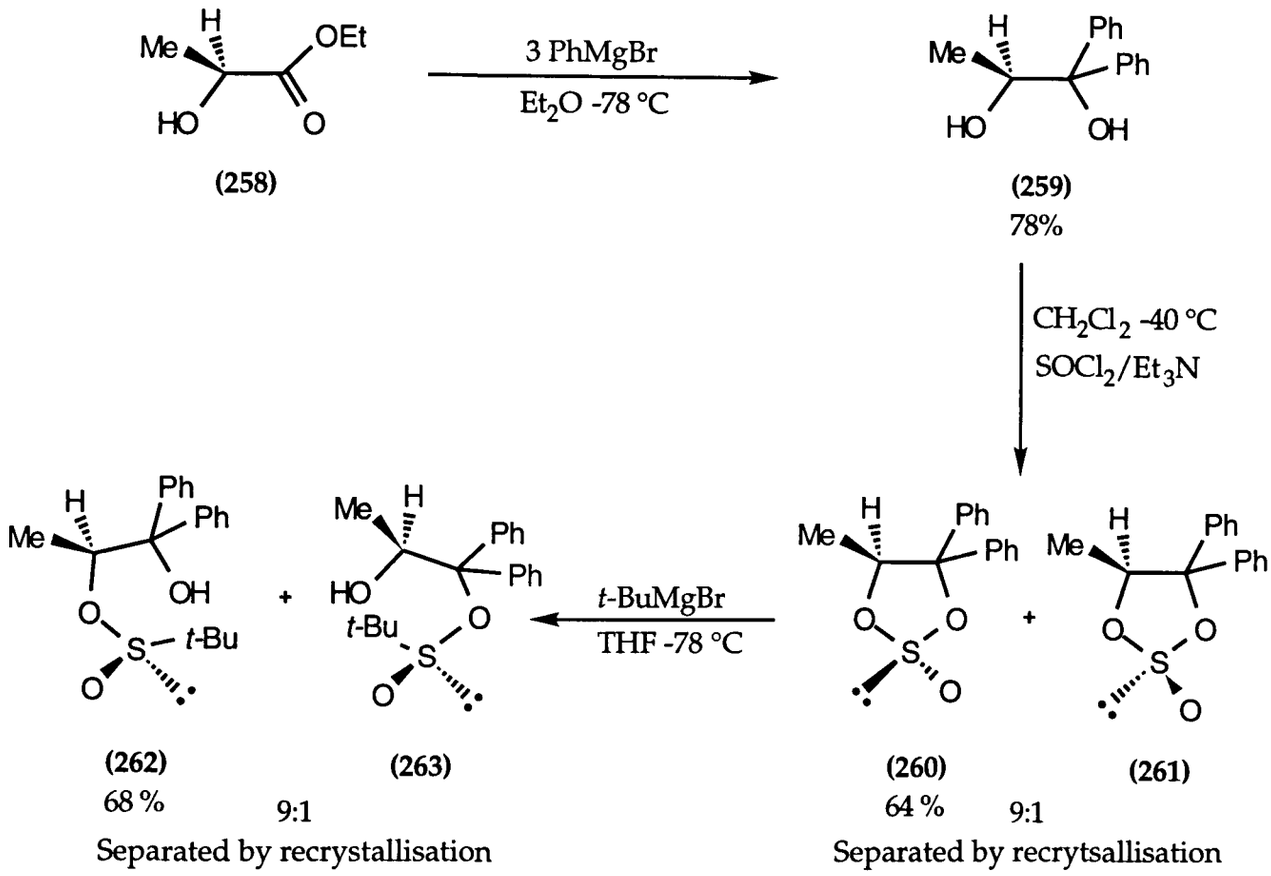
(256) R=Et, 75 % yield, >95 % ee
(257) R=*i*-Pr, 69 % yield, >95 % ee

Scheme 5.1.

As we were interested in the effect that substituents at the sulfoxide centre would have on the stereocontrolling action of α-phosphoryl sulfoxides as catalysts, the bulky *t*-butyl group seemed an obvious choice as a substituent. Although α-phosphoryl *p*-tolyl sulfoxides are readily prepared due to the commercial availability of menthyl *p*-toluenesufinate, the synthesis of other optically active α-phosphoryl sulfoxides is more difficult. The most versatile method for the synthesis of enantiomerically pure sulfoxides is that described by Kagan and Rebiere. This route involves the reaction of organometallic reagents with an enantiomerically pure cyclic sulfite **(260)**. This sulfite was found to react cleanly with many organometallics to give sulfinates with very high regioselectivity. Addition of a second organometallic

transforms the sulfinate in to a chiral sulfoxide with 100 % enantiomeric purity.[193] This route is particularly convenient for the preparation of *t*-butyl sulfoxides.

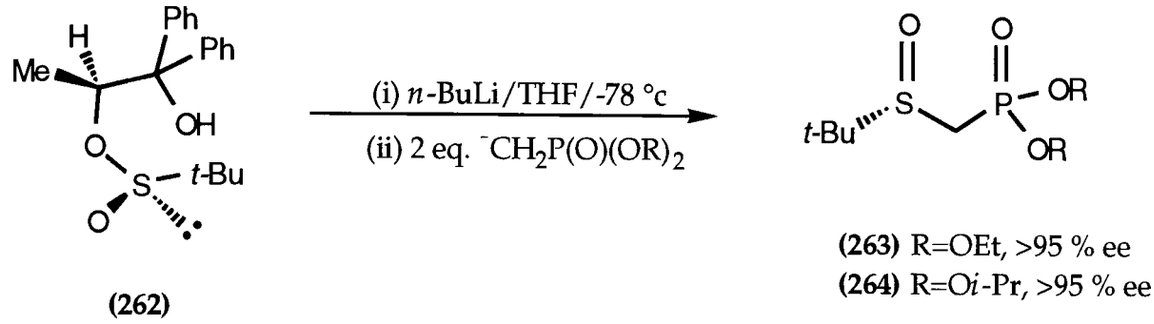
Enantiomerically pure (2*R*,5*S*)-*trans*-4,4-diphenyl-5-methyl-1,3,2-dioxathiolane 2-oxide **(260)** was prepared in two steps from (*S*)-ethyl lactate **(258)** (Scheme 5.2).[193, 194] Reaction of the cyclic sulfite **(260)** with *t*-butylmagnesium chloride afforded pure 2,2-diphenyl-1,2-dihydroxy-propyl 2-*O*-*t*-butylsulfinate **(262)** after one recrystallisation.[193]



Scheme 5.2.

The *t*-butyl sulfinate **(262)** (Scheme 5.3) was first reacted with one equivalent of *n*-butyl lithium to remove the hydroxyl proton. Subsequent treatment with two equivalents of α-lithio dialkyl methanephosphonate yielded the desired dialkyl phosphorylmethyl *t*-butyl sulfoxides **(263-264)** in good yield and high enantiomeric excess. This reaction is known to proceed

with inversion of stereochemistry, resulting in the formation of products with the *S*-configuration at the sulfur atom.[193]



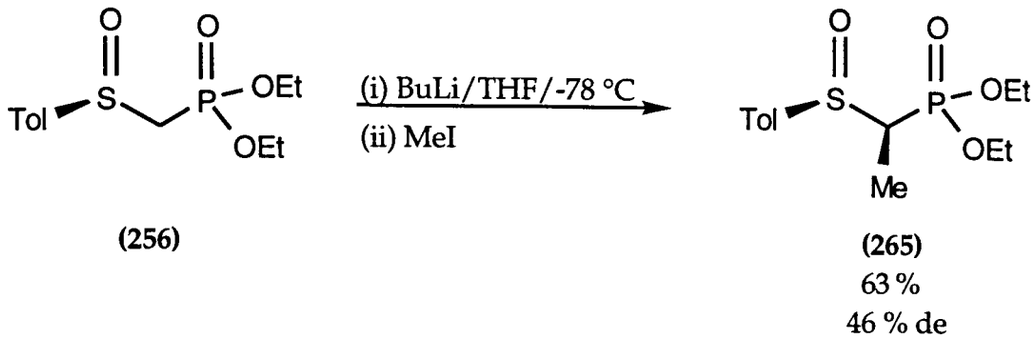
(262)

(263) R=OEt, >95 % ee
(264) R=O*i*-Pr, >95 % ee

Scheme 5.3.

Enantiomeric purities of the α-phosphoryl sulfoxides were determined by the use of the chiral lanthanide shift reagent tris-[3-(trifluoromethylhydroxymethylene-*d*-camphorato]-europium(III) (TFMC), which is known to be suitable for the separation of enantiomeric resonances in α-phosphoryl sulfoxides.[89] All of the α-phosphoryl sulfoxides were determined to be greater than 95 % enantiomerically pure.

The synthesis of S-(*R*),1-(*R*) diethyl α-methylphosphorylmethyl *p*-tolyl sulfoxide **(265)** (Scheme 5.4) was undertaken so that the effect of a catalyst that is chiral at the α-carbon as well as the sulfur could also be investigated. Quenching the lithium salt of (+)-(*S*)-diethyl phosphorylmethyl *p*-tolyl sulfoxide **(256)** with iodomethane gave the α-methylated compound in 65 % yield as a 2.7:1 mixture of the diastereoisomers as determined by ^{31}P nmr spectroscopy. This is in accordance with a 2.5:1 ratio of diastereoisomers prepared from a similar reaction of (+)-(*S*)-dimethyl phosphorylmethyl *p*-tolyl sulfoxide with methyl iodide. Isolation of the major isomer **(265)** was achieved by silica gel chromatography. This isomer was identified as the S-(*R*),1-(*R*) isomer by comparison with the dimethyl phosphonate analogue prepared by Mikolajczyk.[195]



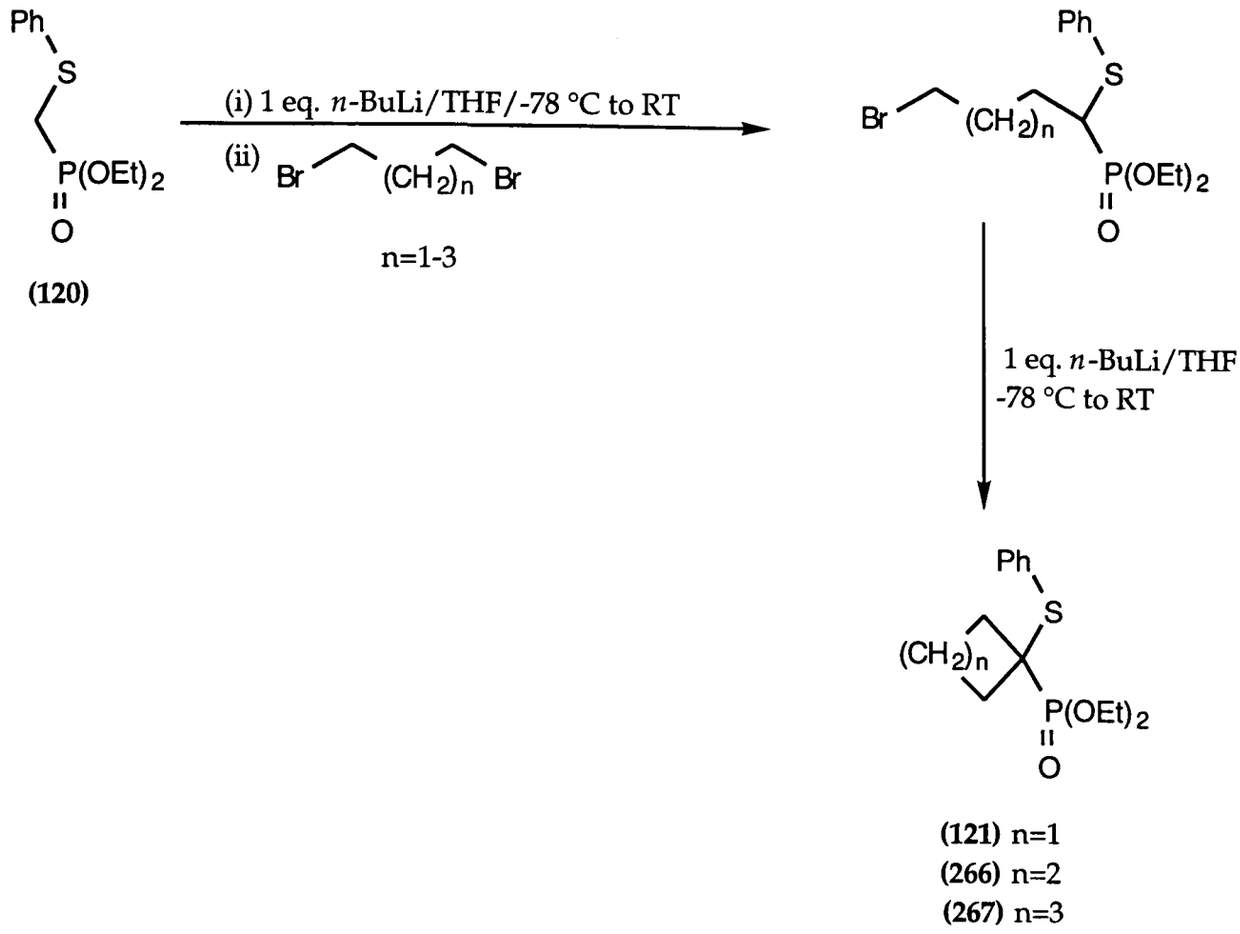
(256)

(265)
63 %
46 % de

Scheme 5.4.

5.4.2. Attempted Synthesis of Cyclic α-Phosphoryl Sulfoxides

In an attempt to investigate the effect of restricting the rotation around the C-S and C-P bonds on the catalytic action of α-phosphoryl sulfoxides, the synthesis of cyclic α-phosphoryl sulfoxides was attempted. As already described in chapter 2, α-phosphoryl sulfoxides can not to be used as malonate analogues in the synthesis of cyclic compounds due to the low reactivity of their α-carbanions under these conditions. However, we have found that the corresponding α-phosphoryl sulfides react with alkyl halides yielding cyclic-1,1-phosphoryl sulfides (Scheme 5.5). Treatment of diethyl phosphorylmethyl phenyl sulfide **(120)** with *n*-butyllithium and a 1,ω-dibromoalkane in THF, followed by a second equivalent of *n*-butyllithium, resulted in high yields of diethyl 1-phenylthiocycloalkane-1-phosphonates **(121, 266-267)**.

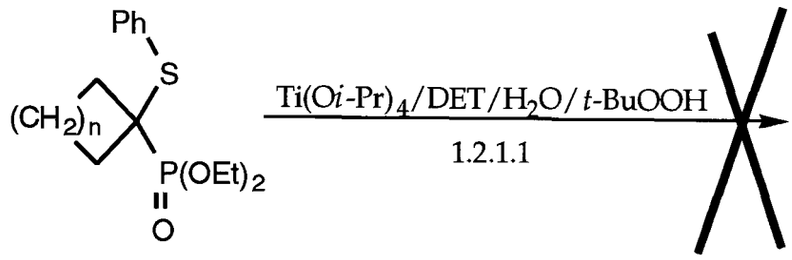


Scheme 5.5.

It was hoped that asymmetric oxidation of the sulfides would afford the optically active sulfoxides. Although several procedures for the chemical asymmetric oxidation of sulfides to give sulfoxides are known, the degree of asymmetric induction is often highly dependent on the nature of the substituents on the sulfur atom.[196] One of the most effective methods for the asymmetric oxidation of sulfides is that described by Kagan *et al.* This procedure uses a modification of the Sharpless epoxidation conditions, in which one equivalent of water is included in the reaction mixture. High enantiomeric excesses have been observed using these conditions.[197]

Treatment of the cyclic-1,1-phosphoryl sulfides **(121, 266-267)** with titanium *iso*-propoxide, diethyl tartrate (DET), water and *t*-butyl hydroperoxide did not result in oxidation of the sulfide (Scheme 5.6). Sulfoxides are known to be good ligands for titanium *iso*-propoxide,[198] and this oxidation reaction is known to be inhibited when one equivalent of a

sulfoxide is present.[197] As phosphoryl oxygen atoms are also known to coordinate to metals,[199] we thought that one reason for the unreactivity of our sulfides might be the co-ordination of the titanium to the phosphoryl oxygen in a fashion to that which it co-ordinates to the sulfoxide. The addition of a second equivalent of titanium *iso*-propoxide or a second equivalent of titanium *iso*-propoxide and DET did not facilitate the oxidation. It is quite probable that the phosphoryl oxygen is co-ordinating to the titanium and sterically preventing any reaction from occurring at the sulfur atom. As a result, we were unable to prepare cyclic-1,1-phosphoryl sulfoxides.

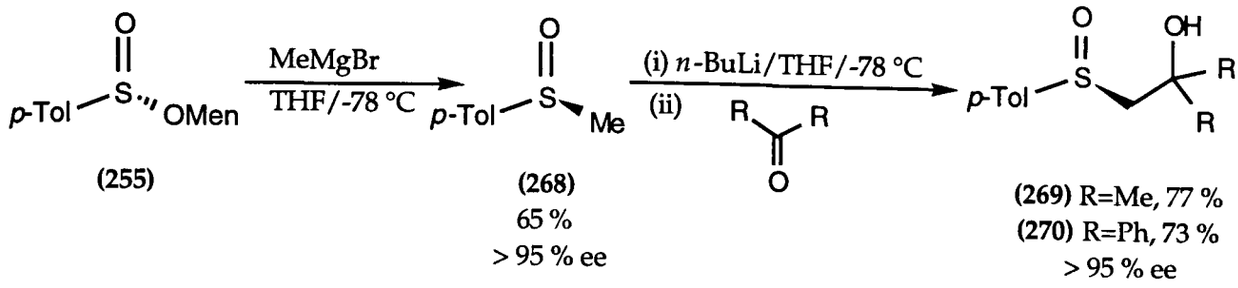


(121) n=1
(266) n=2
(267) n=3

Scheme 5.6.

5.4.3. Synthesis of β-Hydroxy Sulfoxides

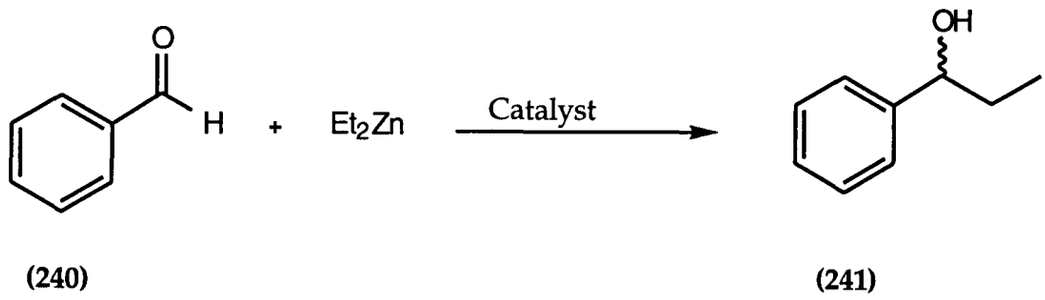
Another class of compounds that we were interested in investigating were β-hydroxy sulfoxides. These compounds are direct analogues of β-hydroxy sulfoximides that have been reported as catalysts for the enantioselective ethyl transfer from diethylzinc to aldehydes. The synthesis of the β-hydroxy *p*-tolyl sulfoxides (Scheme 5.7) was carried out *via* methyl *p*-tolyl sulfoxide **(268)**, which was prepared by treatment of menthyl *p*-toluenesulfinate **(255)** with methylmagnesium iodide. Reaction of α-lithio methyl *p*-tolyl sulfoxide with the appropiate ketone produced the enantiomerically pure β-hydroxy sulfoxides **(269-270)** in high yields.



Scheme 5.7.

5.4.4. The Use of Chiral Sulfoxides as Potential Asymmetric Catalysts

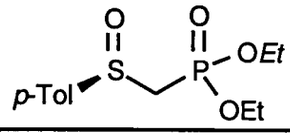
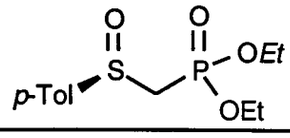
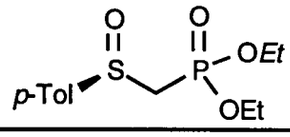
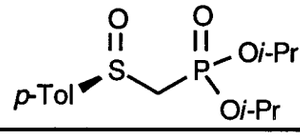
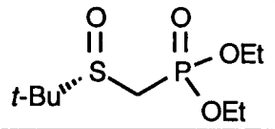
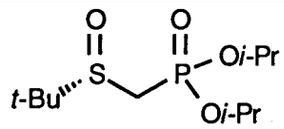
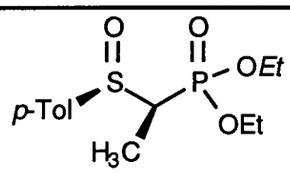
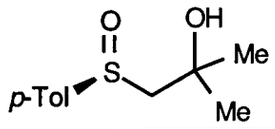
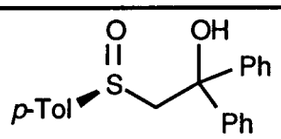
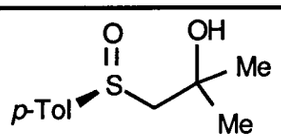
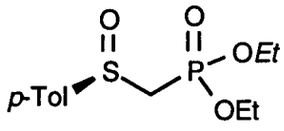
The catalytic activity of the substituted chiral sulfoxides was investigated in the reaction between diethylzinc and benzaldehyde (Scheme 5.8), as these substrates have been used as standard conditions for many investigations of this type. All the reactions were carried out at 0 °C, with a 2:1 ratio of diethylzinc to benzaldehyde and 10 mole % catalyst. The exceptions to this were the control reaction in which there was no catalyst present and reaction 3 in which the ratio of diethylzinc to benzaldehyde to catalyst was 1:1:1. The results of this study are summarised in table 5.1.



Scheme 5.8.

As expected, in the absence of any catalyst little alkylation occurs even after extended reaction times. All the chiral sulfoxides investigated have the ability to catalyse the ethylation of benzaldehyde **(240)** by diethylzinc. Unfortunately this catalytic activity shows no enantioselectivity in any of the cases examined. In the case of the α-phosphoryl sulfoxides, increasing the size of the substituent on the sulfoxide (from phenyl to *t*-butyl) has no effect on the lack of enantioselectivity, but does result in an increase of the reaction time.

Table 5.1: Catalytic Activity of Chiral Sulfoxides

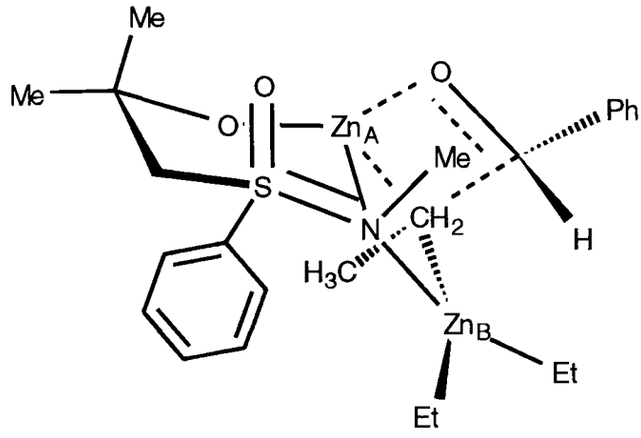
	Catalyst	Mol %	Reaction Time (h)	% Yield	% ee
1	None	-	> 50	< 5	0
2		10	12	100	0
3		100	> 50	0	0
4		10	3	7	0
5		10	12	100	0
6		10	18	95	0
7		10	18	82	0
8		10	18	95	0
9		10	12	100	0
10		10	15	100	0
11	 + $Ti(O i\text{-}Pr)_4$	10	12	100	0
12	 + $Ti(O i\text{-}Pr)_4$	10	12	100	0

Similarly, increasing the size of the phosphonate esters (from ethyl to *iso*-propyl) also increases the reaction time. In the case of the β-hydroxy sulfoxides, increasing the size of the substituents adjacent to the hydroxyl group again increases the reaction time.

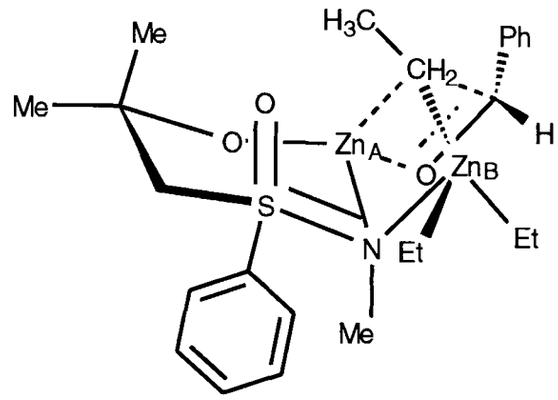
When the catalyst is present in equimolar amounts with the diethylzinc, no alkylation of the aldehyde occurs. The addition of a second equivalent of diethylzinc allows the reaction to proceed. Similar findings have been reported for other catalysts of this reaction,[185, 190] suggesting that the mechanism of catalysis is identical to that described above for DAIB.

Reaction of diethylzinc and benzaldehyde **(240)** with titanium *iso*-propoxide in the presence of a chiral dialkyl thiophosphoramidate results in highly enantioselective addition of the ethyl group.[191] However, under these reaction conditions, in the presence of α-phosphoryl sulfoxides or β-hydroxy sulfoxides no enantioselectivity was observed.

Although all the α-phosphoryl sulfoxides or β-hydroxy sulfoxides investigated were found to catalyse the reaction between diethylzinc and benzaldehyde, this catalytic action was in no case accompanied by enantioselectivity. One explanation for this lack of enantioselectivity results from comparison of the proposed transition state of these compounds with the transition state of other similar compounds that do show enantioselectivity in the catalysis of this reaction for example, β-hydroxy sulfoximides. Assuming that the mechanism of catalysis of β-hydroxy sulfoximides is identical to that proposed for DAIB (Figure 5.5), an analogous transition state complex **(271-272)** for the action of β-hydroxy sulfoximides can be proposed. This transition state complex would involve the formation of a 6/4 fused bicyclic complex (Figure 5.11), similar to the 5/4 system **(248)** described for DAIB.



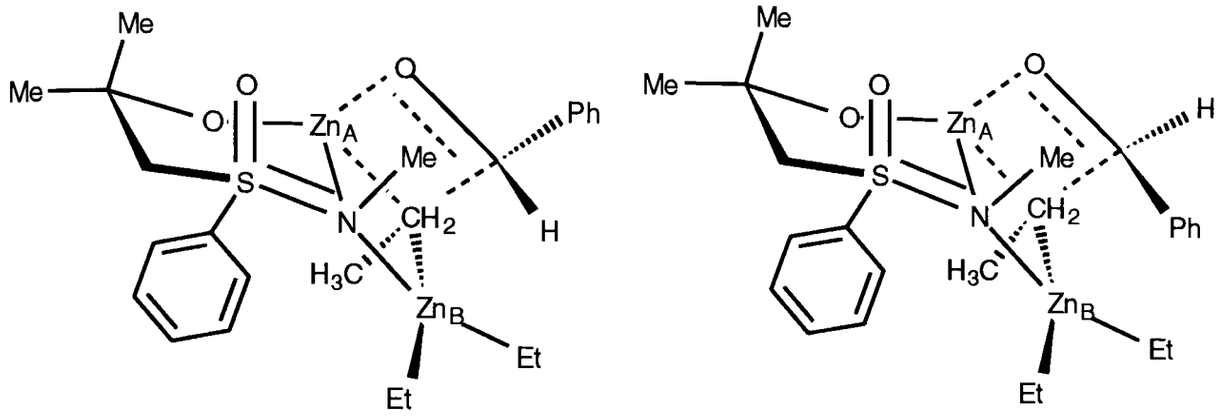
(271)
Less sterically hindered transition state
Lower Energy



(272)
More sterically hindered transition state
Higher Energy

Figure 5.11: Proposed Transition State Complex for the Action β-Hydroxy Sulfoximides

In the case of β-hydroxy sulfoximides, the transition state will involve a 6-membered ring **(271)** which is likely to adopt a twisted chair conformation to minimise steric interactions. The phenyl substituent of the sulfur is likely to adopt the less hindered pseudo-equatorial position. The more stable complex **(271a)** (Figure 5.12) is most likely the one in which the nitrogen methyl is psuedo-equatorial and bulky zinc alkoxide (Zn_B) co-ordinates to the nitrogen in the psuedo-axial position, thus minimising steric interaction between the phenyl group and the zinc alkyl groups. The stereocontrol of this reaction is then due to the non-bonded repulsion of the carbonyl substituents from the terminal alkyl group attached to Zn_B, as described in the case of DAIB, the *S*-directing conformation **(271a)** being more stable than the *R*-directing **(271b)**. This mechanism correctly accounts for the stereochemistry of the reaction diethylzinc and benzaldehyde in the presence of (*S*)-β-hydroxy sulfoximides.[190]

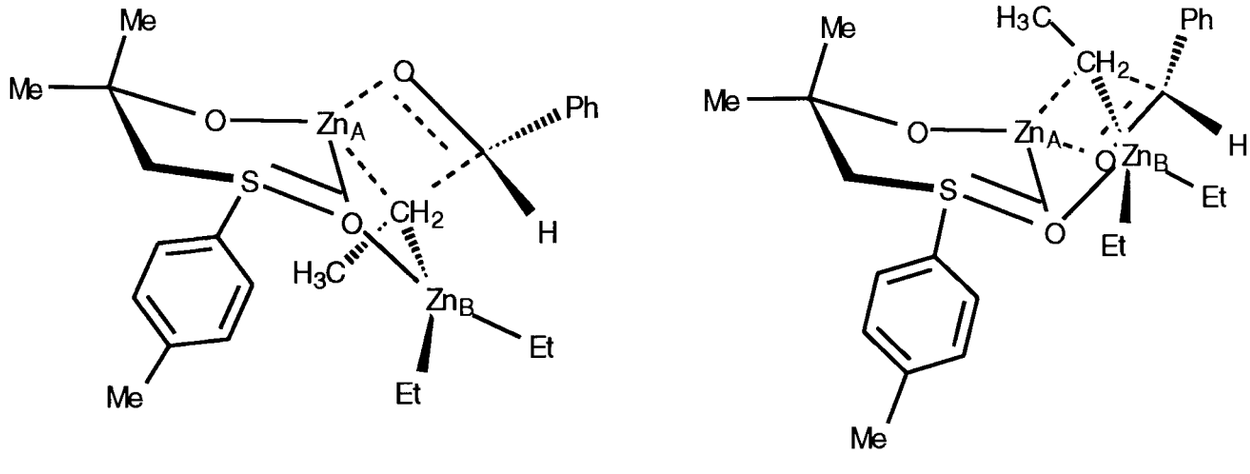


(271a)
S-directing

(271b)
R-directing

Figure 5.12: Stereocontrol of the Reaction Catalysed by (*S*)-β-Hydroxy Sulfoximides

In the case of the β-hydroxy sulfoxides and α-phosphoryl sulfoxides, a similar transition state **(273)** can be proposed (Figure 5.13). However, in the case of these compounds there is no substituent on the oxygen atom that co-ordinates to Zn_B that will interact sterically with the substituent on the chiral sulfur atom. Therefore, there is not likely to be a significant energy difference between the transition state complex **(273)** in which Zn_B is axial and that in which Zn_B is equatorial **(274)**. As these two transition states would lead to the opposite enantiomers, a racemic mixture is formed.



(273)

(274)

Figure 5.13: Proposed Transition State Complexes for Catalysis by Chiral Sulfoxides

5.5. Conclusion

Both α-phosphoryl sulfoxides and β-hydroxy sulfoxides have been shown to catalyse the reaction between diethylzinc and benzaldehyde. Unfortunately this catalytic action is not accompanied by enantioselection. It appears that for compounds which are likely to form a 6-membered transtion state in reactions of this type e.g. β-hydroxy sulfoximides, α-phosphoryl sulfoxides and β-hydroxy sulfoxides, the presence of a substituent on the co-ordinating atom, such as the methyl of the β-hydroxy sulfoximides is essential for enantioselectivity. Further information on the mechanism of the reaction could be gained from the use of sulfimide analogues of the sulfoxides described above.

Chapter 6

Experimental

6.1. General Experimental

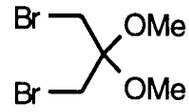
Melting points were determined using a Stuart Scientific SMP 1 melting point apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity Ltd model AA-1000 polarimeter at 589 nm (Na D-line) with a path length of 2 dm. Concentrations (c) are quoted in g/100 cm^3. Microanalyses were performed at the University of Warwick. Infra red spectra were recorded neat, or as nujol mulls, as indicated, on a Perkin-Elmer 1720X fourier transform spectrometer using sodium chloride plates. Only selected absorbances (ν_{max}) are reported. ^1H nmr spectra were recorded at either 250 MHz or 400 MHz on Bruker ACF 250 or Bruker ACP 400 instruments respectively. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced externally to tetramethylsilane (TMS) at 0 ppm. Coupling constants (J) are reported in Hertz. ^{13}C nmr spectra were recorded at 62.9 MHz on a Bruker ACF 250 instrument or 100.6 MHz on a Bruker ACP 400 instrument. Chemical shifts (δ_C) are quoted in ppm, referenced externally to TMS. Coupling constants (J_{CP}) are reported in Hertz. ^{31}P nmr spectra were recorded at 162 MHz or 101 MHz on a Bruker ACP 400 or Bruker ACF 250 instrument, respectively. Chemical shifts (δ_P) are quoted in parts per million (ppm), referenced externally to 85 % phosphoric acid at 0 ppm. ^{19}F nmr spectra were recorded at 376.3 MHz on a Bruker ACP 400 instrument. Chemical shifts (δ_F) are quoted in parts per million (ppm), referenced to trifluoroacetic acid at 0 ppm. All mass spectra were recorded on Kratos MS 90 spectrometer with only molecular ions (M^+) and major peaks being reported, with intensities quoted as percentages of the base peak. Chemicals were purchased from Aldrich, Fluka or Sigma at the highest available grade. All solvents were purchased

from Fisons Scientific Equipment at SLR grade and purified, when required, by literature methods.[200] Anhydrous solvents were obtained as follows: dichloromethane, distilled from calcium hydride under nitrogen; THF and dioxan, distilled from sodium-benzophenone ketal under nitrogen; methanol, distilled from magnesium methoxide under nitrogen; DMF, distilled from calcium hydride under nitrogen; acetone, distilled from magnesium sulfate under nitrogen; pyridine, distilled from sodium hydroxide under nitrogen. Tlc was performed on aluminium backed plates pre-coated with silica (0.2 mm, $60F_{254}$) which were developed using one or more of the following agents: UV fluoresence (254 nm), iodine vapour, potassium permanganate solution (0.5 % *v/v*), ammonium molybdate (2.5 % *w/v*), *p*-anisaldehyde (2.5 % *v/v*) or ninhydrin (0.2 % *w/v*). Flash chromatography was performed on silica gel (Merck Kieselgel $60F_{254}$, 230-400 mesh).

X-ray crystallographic measurements were made with a Siemens P3R3 four-circle diffractometer equipped with an Oxford Cryosystems Cooler (version 2.4). Graphite monochromated Mo-Kα radiation (λ 0.71073 Å) was used to collect the intensity data in the ω-2θ mode. Unit cell parameters and orientation were obtained by least-squares refinement of the setting angles of 20 high angle reflections. The crystallographic program system was SHELXTL-93. The structures were solved by direct methods and refined using full-matrix least-squares on F^2. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were given isotropic thermal parameters equal to 1.2 (or 1.5 for methyl groups) times the equivalent isotropic displacement parameter of the atom to which it is attached. A summary of the crystal data, refinement details, bond lengths and angles are given in the appendices.

6.2. Synthesis of Amino Cyclobutane Phosphonic Acids

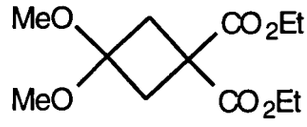
6.2.1. 1,3-Dibromoacetone-2,2-dimethoxypropane (92)



(92)

Acetone (30g, 0.52 mol) was added to methanol (250 cm^3) in a 1 dm^3 flask equipped with a dropping funnel and condenser. The reaction mixture was cooled in ice, and bromine (166g, 1.04 mol) was slowly added to the reaction mixture with stirring. After the addition was complete the reaction mixture was stirred for a further 12 h, producing colourless crystals of the desired product which were removed by filtration, washed with a small amount of water and dried under vacuum (112.68 g, 83 %). m.p. 65-67 °C (lit.,[81] 65-67 °C) δ_H (250 MHz; $CDCl_3$) 3.3 (4H, s, CH_2Br), 3.55 (6H, s, OCH_3); δ_C (63 MHz; $CDCl_3$) 30.12 (CH_2Br), 49.13 (OCH_3), 49.58 ($C(OCH_3)_2$).

6.2.2. Diethyl 3,3-Dimethoxycyclobutane-1,1-dicarboxylate (95)

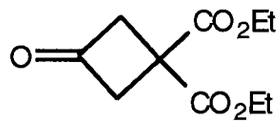


(95)

Diethyl malonate (49 g, 0.306 mol) was added dropwise to a stirred suspension of NaH (10 g, 80 %oil emulsion, 0.31 mol) in anhydrous DMF (250 cm^3) under an atmosphere of nitrogen. On cessation of hydrogen evolution, 1,3-dibromoacetone-2,2-dimethoxypropane **(92)** (36 g, 0.138 mol) was added in one portion. The mixture was heated at 121-128 °C for 48 h. The cooled reaction mixture was poured into an saturated solution of ammonium chloride (100 cm^3) and extracted with dichloromethane (5 x 100 cm^3). The combined

organic extracts were washed with water (2 x 100 cm^3), aqueous sodium bicarbonate (2 x 100 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to give a yellow oil. The crude mixture was distilled under reduced pressure to give the desired compound (18 g, 45 %). b.p. 108-110 °C, 0.1 mm Hg (lit.,[75] 92 °C, 0.5 mm Hg) ϑ_{max}/cm^{-1} (neat) 2984, 2959, 1736, 1466, 1447, 1283, 1196, 1142, 1075; δ_H (250 MHz; $CDCl_3$) 1.32 (6H, t, OCH_2CH_3), 2.68 (4H, s, C(2)-H & C(4)-H), 3.24 (6H, s, OCH_3), 4.3 (4H, q, *J* 5.3, OCH_2CH_3); δ_C (250 MHz; $CDCl_3$) 13.94 (OCH_2CH_3), 39.46 (C-2 & C-4), 44.46 (C-1), 48.01 (OCH_3), 60.79 (OCH_2CH_3), 98.21 (C-3), 169.65 (C=O); (NH_3 CI) *m/z* 278 ($[M+18]^+$, 10 %), 246 (80), 229 (100), 214 (40), 187 (25), 155 (30), 113 (30), 88 (100).

6.2.3. Diethyl 3-Oxocyclobutane-1,1-dicarboxylate (96)

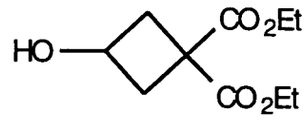


(96)

Diethyl 3,3-dimethoxycyclobutandicarboxylate **(95)** (5 g, 16 mmol) was dissolved in dichloromethane (20 cm^3) and trimethylsilyl iodide (4 g, 20 mmol) was added to the solution under an atmosphere of nitrogen. The reaction was stirred at room temperature for 1 h at which time analysis by nmr spectroscopy indicated that the reaction had gone to completion. The reaction mixture was poured into methanol (10 cm^3) and the solution was evaporated to dryness under reduced pressure. The residue was disolved in ether and washed with aqueous sodium bisulfite (3 x 15 cm^3), saturated sodium bicarbonate solution (2 x 10 cm^3) and brine (2 x 10 cm^3). The organic solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield the title compound **(96)** as a colourless oil which was purified by Kugelrohr distillation (4.05 g, 98 %). b.p. 150-155 °C, 0.1 mm Hg

(lit.,[80] 112-113 °C, 3 mm Hg) ϑ_{max}/cm^{-1} (neat) 2985, 2940, 1806, 1736, 1449, 1370, 1280, 1220, 1180, 1097; δ_H (250 MHz; $CDCl_3$) 1.28 (6H, t, *J* 5.5, OCH_2CH_3), 3.65 (4H, s, C(2)-H & C(4)-H), 4.28 (4H, q, *J* 5.5, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 14.07 (OCH_2CH_3), 37.12 (C-1), 51.23 (C-2 & C-4), 60.71 (OCH_2CH_3), 173.74 (C=O), 201.45 (C(3) C=O); (NH_3 CI) *m/z* 232 (55, $[M+18]^+$, 23 %), 215 ($[M+H]^+$, 80), 141 (20), 79 (100).

6.2.4. Diethyl 3-Hydroxycyclobutanedicarboxylate (97)

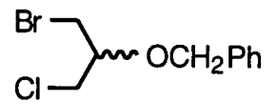


(97)

Diethyl 3-oxocyclobutanedicarboxylate **(96)** (4.1 g, 19 mmol) was dissolved in ethanol (20 cm^3) and sodium borohydride (800 mg, 22 mmol) was added in one portion. The reaction was stirred at room temperature for 3 h. Analysis by tlc (petroleum ether/ethyl acetate 4:1) indicated no reaction had occurred. The reaction mixture was heated to reflux for 5 h at which time tlc indicated that no starting material remained. The reaction mixture was cooled to room temperature and quenched by the addition of saturated ammonium chloride solution (10 cm^3). The ethanol was removed under reduced pressure and the aqueous solution extracted with ether (3 x 20 cm^3). The combined ethereal layers were washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure to afford the crude compound which was purified by silica gel chromatography (petroleum ether/ethyl acetate 4:1) to yield the title compound **(97)** as a colourless oil (1 g, 25 %). (154-158 °C, 0.1 mmHg) (lit.,[80] 178-183 °C 3 mmHg) ϑ_{max}/cm^{-1} (neat) 3462, 2986, 2947, 1733, 1424, 1271, 1181; δ_H (250 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.5, OCH_2CH_3), 2.43 (2H, C(2)-H & C(4)-H), 2.85 (2H, m, C(2)-H' & C(4)-H'), 4.2 (4H, q, *J* 7.5, OCH_2CH_3), 4.35 (1H, m, C(3)-

H); δ_C (250 MHz; $CDCl_3$) 13.81 (OCH_2CH_3), 40.00 (C-2 & C-4), 45.63 (C-1), 61.50 (C-3), 61.78 (OCH_2CH_3), 171.31 (C=O), 171.61 (C=O); (EI) *m/z* 216 (M^+, 10 %), 171 (33), 143 (43), 127 (58), 113 (16), 97 (100), 86 (16), 69 (44), 43 (47).

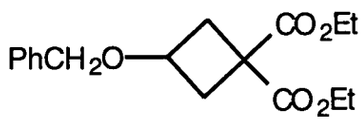
6.2.5. 1-Chloro-2-benzyloxy-3-bromopropane (91)



(91)

Epichlorohydrin (102 g, 1.1 mol) was added to a solution of mercuric chloride (0.2 g, 0.74 mmol) in benzyl bromide (171 g, 1 mol). The reaction mixture was heated to 160 °C, with stirring, for 24 h and then cooled to room temperature. Distillation under reduced pressure yielded the desired compound **(91)** (140-145 °C, 0.2 mmHg) (lit.,[80] 148-155 °C, 0.2 mmHg. (189 g, 69 %). δ_H (250 MHz; $CDCl_3$) 3.56 (2H, m, CH_2Cl), 3.72 (2H, m, CH_2Br), 3.81 (1H, m, CH), 4.67 (2H, Broad s, PhCH_2), 7.38 (5H, br. s, ArH); δ_C (63 MHz; $CDCl_3$) 31.71 (CH_2Br), 44.03 (CH_2Cl), 72.26 ($CHOCH_2Ph$), 77.36 (CH_2Ph), 127.65, 128.09, 128.52, 137.19 (6C, Ar); (EI) *m/z* 263 (M^+, 100 %), 182 (56), 146 (31), 91 (43), 77 (53), 65 (42).

6.2.6. Diethyl-3-(Benzyloxy)cyclobutanedicarboxylate (98)

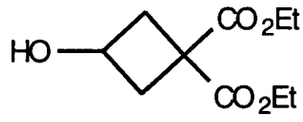


(98)

Diethyl malonate (80 g, 0.5 mol) was added dropwise to a suspension of sodium hydride (15 g, 80 % oil emulsion, 0.5 mol) in anhydrous dioxane (400 cm^3) under an atmosphere of nitrogen. The reaction mixture was stirred until the evolution of hydrogen ceased. 1-Chloro-2-benzyloxy-3-bromopropane **(91)** (132.2 g, 0.5 mol) was added dropwise to the reaction

mixture. After the addition was complete the reaction mixture was heated to reflux for 24 h. After cooling the reaction mixture to room temperature a further portion of sodium hydride (15 g, 0.5 mol) was added. The reaction mixture was heated to reflux for a further 48 h, then cooled to room temperature poured into water (600 cm^3) and extracted with ether (4 x 100 cm^3). The organic extracts were combined and washed with water (2 x 100 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was distilled under reduced pressure to yield the title compound **(99)** (81.2 g, 53 %) (150-160 °C, 0.1 mmHg) (lit.,[80] 178-183 °C 0.2 mmHg) δ_H (250 MHz; $CDCl_3$) 1.61 (6H, t, *J* 7.5, OCH_2CH_3), 3.8 (4H, m, C(2)-H_2 & C(4)-H), 4.22 (4H, q, *J* 7.5, OCH_2CH_3), 4.36 (1H, m, C(3)-H), 4.45 (2H, s, $ArCH_2$), 7.35 (5H, m, PhH); δ_C (63 MHz; $CDCl_3$) 13.81 (OCH_2CH_3), 38.07 (C-2 & C-4), 46.51 (C-1), 61.77 (OCH_2CH_3), 61.93 (OCH_2CH_3), 69.85 (C-3), 77.48 (CH_2Ph), 127.82, 128.57, 137.22 (6C, Ar), 171.27 (C=O), 171.59 (C=O); (EI) *m/z* 306 (M^+, 8%), 277 (19), 215 (24), 201 (91), 173 (100).

6.2.7. Diethyl 3-Hydroxycyclobutanedicarboxylate (97)

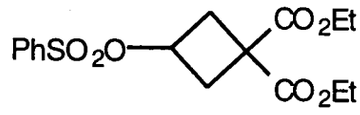


(97)

A solution of diethyl 3-benzyloxycyclobutandicarboxylate **(99)** (30.6 g, 0.1 mol) in methanol was hydrogenated over and palladium on carbon for 6h (3 atmospheres). The catalyst was removed by filtration through celite which was washed with methanol (2 x 30 cm^3). The solvent was removed under reduced pressure to afford diethyl 3-hydroxycyclobutanedicarboxylate (21.5 g, 98 %). (154-158 °C, 0.1 mmHg) (lit.,[80] 178-183 °C 3 mmHg) ϑ_{max}/cm^{-1} (neat) 3462, 2986, 2947, 1733, 1424, 1371, 1271, 1181; δ_H (250 MHz; $CDCl_3$) 1.23 (6H, t,

J 7.5, OCH_2CH_3), 2.43 (2H, C(2)-H & C(4)-H), 2.85 (2H, m, C(2)-H' & C(4)-H'), 4.2 (4H, q, *J* 7.5, OCH_2CH_3), 4.35 (1H, m, *CH*OH); δ_C (63 MHz; $CDCl_3$) 13.81 (OCH_2CH_3), 40.00 (C-2 & C-4), 45.63 (C-1), 61.50 (C-3), 61.78 (OCH_2CH_3), 171.31 (C=O), 171.61 (C=O); (EI) *m/z* 216 (M^+, 10 %), 171 (33), 143 (43), 127 (58), 113 (16), 97 (100), 86 (16), 69 (44), 55 (10), 43 (47).

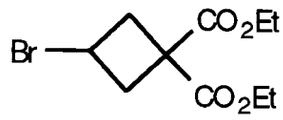
6.2.8. Diethyl 3-(Benzenesulfonyloxy)cyclobutane-1,1-dicarboxylate (99)



(99)

A solution of diethyl 3-hydroxycyclobutanedicarboxylate **(97)** (10g, 46 mmol) and benzenesulfonyl chloride (9.1 g, 52 mmol) under an atmosphere of nitrogen was cooled to 0 °C in an ice bath. Anhydrous pyridine (50 cm^3) was added slowly, the reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to room temperature with stirring for 12h. The reaction mixture was poured into water (100 cm^3) and extracted with ether (3 x 50 cm^3). The ethereal extracts were washed with water (3 x 50 cm^3), dilute hydrochloric acid (2 x 50 cm^3) and brine (2 x 30 cm^3). The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced vacuum to yield the desired product **(99)** (15 g, 91%). ϑ_{max}/cm^{-1} (neat) 2984, 1731, 1370, 1273, 1191, 1112, 1096, 1022; δ_H (250 MHz; $CDCl_3$) 1.22 (6H, t, *J* 7.5, OCH_2CH_3), 2.74 (4H, m, C(2)-H & C(4)-H), 4.15 (4H, q, *J* 7.5, OCH_2CH_3), 4.93 (1H, quint, *J* 5.1, C(3)-H), 7.60 (3H, m, ArH), 7.85 (2H, m, ArH); δ_C (63 MHz; $CDCl_3$) 13.97 (OCH_2CH_3), 37.43 (C-2 & C-4), 46.29 (C-1), 61.72 (OCH_2CH_3), 61.92 (OCH_2CH_3), 69.05 (C-3), 127.64, 127.73, 129.26, 133.92 (6C, Ar), 169.73 (C=O), 170.58 (C=O); (NH_3 CI) *m/z* 374 ($[M+NH_4]^+$, 100 %), 357 ($[M+H]^+$, 55), 283 (18), 235 (12), 224 (21), 199 (49), 141 (17).

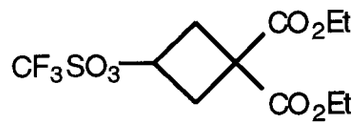
6.2.9. Diethyl 3-Bromocyclobutane-1,1-dicarboxylate (100)



(100)

Diethyl 3-(benzenesulfonyloxy)cyclobutanedicarboxylate **(99)** (6g, 19.6 mmol) was added to a solution of anhydrous acetone (100 cm^3). Fused lithium bromide (4.2 g, 49 mmol) was added in one portion. The reaction mixture was heated to reflux, with stirring, for 48 h under an atmosphere of nitrogen. The solvent was removed under reduced vacuum and the residue was dissolved in ether (100 cm^3) and washed with water (3 x 30 cm^3) and brine (2 x 20 cm^3). The organic fraction was dried over anhydrous $MgSO_4$, filtered and the solvent removed to yield the title compound as a colourless oil **(100)** (5.2 g, 95 %). ϑ_{max}/cm^{-1} (neat) 2983, 1733, 1272, 1177, 1157, 1121; δ_H (250 MHz; $CDCl_3$) 1.30 (6H, t, *J* 7.5, OCH_2CH_3), 2.76 (2H, m, C(2)-H & C(4)-H), 2.94 (2H, m, C(2)-H' & C(4)-H'), 4.24 (4H, q, *J* 7.5, OCH_2CH_3), 5.02 (1H, m, *CH*Br); δ_C (60 MHz; $CDCl_3$) 13.92 (OCH_2CH_3), 38.37 (C-2 & C-4), 46.62 (C-1), 61.71 (OCH_2CH_3), 61.98 (OCH_2CH_3), 62.18 (C-3), 170.11 (C=O), 170.86 (C=O); (EI) *m/z* 281 (M^+, 37 %), 233 (39), 199 (100), 153 (40), 125 (26), 97 (21), 53 (19).

6.2.10. Diethyl 3-(Trifluoromethanesulfonyloxy)cyclobutane-1,1-dicarboxylate (106)

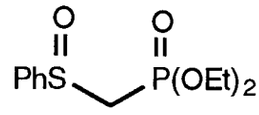


(106)

A solution of diethyl 3-hydroxycyclobutanedicarboxylate **(97)** (2 g, 9.2 mmol) and pyridine (5 cm^3) in dichloromethane (20 cm^3) was cooled to -5 °C

under an atmosphere of nitrogen. Trifluoromethanesulfonic anhydride (3.45 g, 11.0 mmol) was added slowly, then the reaction mixture was gradually allowed to warm to room temperature with stirring. After 12 h, ice water (20 cm^3) was added and the reaction mixture was extracted with dichloromethane (3 x 20cm^3). The combined organic extracts were washed with water (2 x 30 cm^3) and brine (2 x 30 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield the desired product **(106)** as a colourless oil (2.85 g, 89 %). δ_H (250 MHz; $CDCl_3$) 1.18 (6H, t, *J* 7.5, OC_2CH_3), 2.81 (2H, m, C(2)-H & C(4)-H), 3.05 (2H, br m, C(2)-H' & C(4)-H'), 4.15 (q, *J* 7.5, 4H, OCH_2CH_3), 5.3 (1H, quint, *J* 7.45, C-3); δ_C ($CDCl_3$) 13.67 (OCH_2CH_3), 37.67 (C-2 & C-4), 45.70 (C-1), 61.94 (OCH_2CH_3), 62.14 (OCH_2CH_3), 75.87 (C-3), 118.21 (q, *J* 319, SO_3CF_3), 169.26 (C=O), 170.06 (C=O); (NH_3 CI) *m/z* 366 ($[M+18]^+$, 93), 349 ($[M+H]^+$, 40 %), 284 (21), 235 (25), 199 (100), 148 (31), 80 (35).

6.2.11. Diethyl Phosphorylmethyl Phenyl Sulfoxide (115)

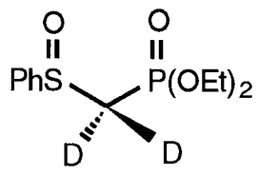


(115)

A solution of sodium metaperiodate (17.2 g, 80 mmol) in water (150 cm^3) was added dropwise to a solution of diethyl phosphorylmethyl phenyl sulfide (20 g, 77 mmol) in acetone (100 cm^3) at 0 °C. The reaction mixture was stirred at -5 °C for 5 h and then at room temperature for 12 h. The acetone was removed under reduced pressure and the aqueous solution extracted with dichloromethane (2 x 100 cm^3, 3 x 50 cm^3). The combined organic extracts were washed with water (2 x 100 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether 4:1) to yield the title

compound as a colourless oil (16 g, 76 %). δ_H (250 MHz; $CDCl_3$) 1.19 (6H, m, OCH_2CH_3), 3.16 (2H, ABX system, J_{AB} 14.53, J_{AX} 16.35, J_{BX} 14.9, SCH_2P), 3.97 (4H, m, OCH_2CH_3), 7.45 (3H, m, Ar), 7.65 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 16.08 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 53.62 (d, J_{CP} 138.8, CH_2P), 62.57 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 124.08, 129.20, 131.53, 144.65 (6C, Ar); δ_P (101 MHz; $CDCl_3$) 16.53; (EI) *m/z* 276 (M^+, 52 %), 248 (24), 220 (53), 172 (21), 125 (100), 95 (59), 77 (48), 65 (37).

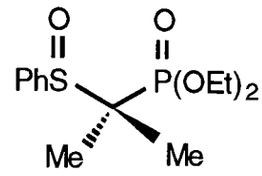
6.2.12. [1,1-^{2}H]-Diethyl Phosphorylmethyl Phenyl Sulfoxide (115a)



(115a)

A solution of diethyl phosphorylmethyl phenyl sulfoxide **(115)** (100 mg, 0.36 mmol) in dry THF (10 cm^3) under an atmosphere of nitrogen at room temperature, was treated with *n*-butyllithium (0.29 cm^3, 0.73 mmol) for 10 min. The reaction mixture was quenched with deuterium oxide (1 cm^3). The THF was removed by evaporation under reduced pressure. The aqueous solution was diluted with water (10 cm^3) and extracted with dichloromethane (3 x 10 cm^3). The combined organic extracts were washed with water (2 x 10cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether 4:1) to yield the title compound **(115a)** (74 mg, 73 %). δ_H (250 MHz; $CDCl_3$) 1.18 (6H, m, OCH_2CH_3), 3.16 (<0.2H, residual protons from SCH_2P), 3.95 (4H, m, OCH_2CH_3), 7.43 (3H, m, Ar), 7.63 (2H, m, Ar); (EI) *m/z* 278 (M^+, 34 %), 250 (28), 222 (51), 174 (23), 125 (100), 95 (65), 77 (46), 65 (35).

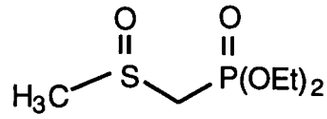
6.2.13. Diethyl 1-Phosphoryl(1-methylethyl) Phenyl Sulfoxide (118)



(118)

A solution of diethyl phosphorylmethyl phenyl sulfoxide **(115)** (100 mg, 0.36 mmol) in dry THF (10 cm^3) at room temperature under an atmosphere of nitrogen, was treated with *n*-butyllithium (0.29 cm^3, 0.73 mmol) for 10 min. The reaction mixture was cooled to -78 °C and iodomethane (0.2 cm^3) was added. The reaction mixture was warmed to room temperature and quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed by evaporation under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 10 cm^3). The combined organic extracts were washed with water (2 x 10cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether 4:1) to yield the title compound **(118)** (71 mg, 65 %). δ_H (250 MHz; $CDCl_3$) 1.20 (3H, d, *J* 4.6, C(1)-CH_3), 1.23 (3H, d, *J* 4.6, C(1)-CH_3), 1.27 (6H, m, OCH_2CH_3), 4.12 (4H, m, OCH_2CH_3), 7.23 (3H, m, Ar), 7.41 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 16.16 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 22.35 (d, $^2J_{CP}$ 5.8, $CHCH_3$), 22.87 (d, $^2J_{CP}$ 5.8, $CHC''H_3$), 53.54 (d, J_{CP} 138.8, SCH_2P), 62.57 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 124.05, 129.48, 131.51, 144.66 (6C, Ar); δ_P (250 MHz; $CDCl_3$) 25.14; (EI) *m/z* 304 (M^+, 48 %), 276 (26), 248 (53), 204 (23), 164 (26), 125 (100), 95 (54), 77 (43), 65 (33).

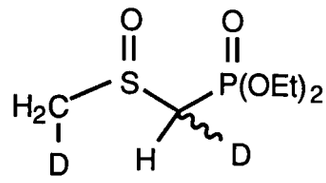
6.2.14. Diethyl Phosphorylmethyl Methyl Sulfoxide (119)



(119)

A solution of sodium metaperiodate (5.7 g, 26.5 mmol) in water (50 cm^3) was added dropwise to a solution of diethyl phosphorylmethyl methyl sulfide (5 g, 25.3 mmol) in acetone (30 cm^3) at 0 °C. The reaction mixture was stirred at -5 °C for 5 h and then at room temperature for 12 h. The acetone was removed under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 50 cm^3). The combined organic extracts were washed with water (2 x 50 cm^3) and brine (2 x 50 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate) to yield the title compound **(119)** (4.4 g, 81 %). δ_H (250 MHz; $CDCl_3$) 1.01 (6H, m, OCH_2CH_3), 2.61 (3H, s, CH_3S), 3.19 (2H, ABX system, J_{AB} 14.50, J_{AX} 15.63, J_{BX} 14.35, CH_2P), 3.88 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 15.99 (d, $^3J_{CP}$ 6.0, OCH_2CH_3), 40.84 (d, $^3J_{CP}$ 4.2, CH_3S), 51.94 (d, J_{CP} 138.8, SCH_2P), 62.52 (d, $^2J_{CP}$ 6.2, OCH_2CH_3); δ_P (101 MHz; $CDCl_3$) 16.18; (EI) *m/z* 214 (M^+, 13 %), 197 (11), 169 (21), 152 (94), 125 (100), 108 (73), 97 (93), 81 (61).

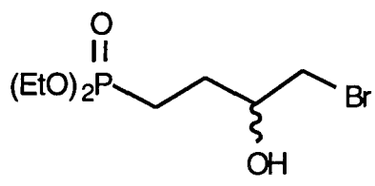
6.2.15. Diethyl Phosphoryl-[^{2}H]-methyl [^{2}H]-Methyl Sulfoxide (119a)



(119a)

A solution of diethyl phosphorylmethyl methyl sulfoxide **(119)** (100 mg, 0.47 mmol) in dry THF (10 cm^3) under an atmosphere of nitrogen was treated with *n*-butyllithium (0.37 cm^3, 0.94 mmol) at room temperature for 10 min. The reaction mixture was quenched with deuterium oxide (1 cm^3). The THF was removed by evaporation under reduced pressure. The aqueous solution diluted with water (10 cm^3) and extracted with dichloromethane (3 x 10 cm^3). The combined organic extracts were washed with water (2 x 10cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate) to yield the title compound **(119a)** (59 mg, 58 %). δ_H (250 MHz; $CDCl_3$) 1.02 (6H, m, OCH_2CH_3), 2.63 (2H, br. s, CH_2[^{2}H]S), 3.18 (1H, m, SC*H*[^{2}H]P), 3.88 (4H, m, OCH_2CH_3); (EI) *m/z* 216 (M^+, 11 %), 171 (28), 153 (94), 127 (100), 110 (73).

6.2.16. Diethyl 3-Hydroxy-4-bromobutanephosphonate (128)

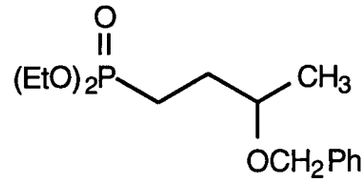


(128)

Diethyl trimethylsilylmethylphosphonate (500 mg, 2.2 mmol) in a solution of anhydrous THF (15 cm^3) under an atmosphere of nitrogen at -78 °C, was treated with *n*-butyllithium (0.9 cm^3, 2.3 mmol). The reaction mixture was stirred at -78 °C for 30 min and epibromohydrin (320 mg, 2.4 mmol) in

anhydrous THF (2 cm^3)was added. The reaction mixture was warmed to room temperature and then heated to reflux for 5 h. After cooling to room temperature the reaction was quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed by evaporation under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 10 cm^3). The combined organic extracts were washed with water (2 x 10cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether 10:1) to afford the title compound **(128)** (262 mg, 40 %). δ_H (250 MHz; $CDCl_3$) 1.08 (6H, t, *J* 6.8, OCH_2CH_3), 1.64 (4H, m, C(2)-H & C(1)-H), 3.41 (2H, m, C(3)-H) 3.64 (1H, m, C(4)-H_2), 4.05 (4H, m, OCH_2CH_3); δ_C (250 MHz; $CDCl_3$) 13.24 (d, J_{CP} 137.3, C-1), 16.02 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 28.61 (d, $^2J_{CP}$ 4.8, C-2), 41.32 (C-4), 62.31 (d, $^2J_{CP}$ 5.9, OCH_2CH_3), 69.81 ($^3J_{CP}$ 6.4, C-3); (EI) *m/z* 398 (M^+, 46 %), 396 (45), 370 (23), 342 (18), 217 (56), 189 (22), 125 (100), 77 (25).

6.2.17. Diethyl 3-Benzyloxy-4-chlorobutanephosphonate (130)

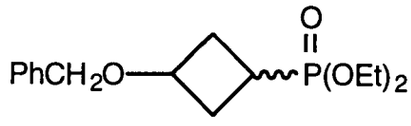


(130)

Diethyl methanephosphonate (500 mg, 3.3 mmol) in a solution of anhydrous THF (15 cm^3) at -78 °C under an atmosphere of nitrogen, was treated with *n*-butyllithium (1.3 cm^3, 3.3 mmol). The reaction mixture was stirred at -78 °C for 1 h and 1-chloro-2-benzyloxy-3-bromopropane (895 mg, 3.4 mmol) in anhydrous THF (2 cm^3) was added. The reaction mixture was warmed to room temperature for 1 h and then cooled to -78 °C. A second equivalent of *n*-butyllithium (1.3 cm^3, 3.3 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The

reaction was quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed by evaporation under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 10 cm^3). The combined organic extracts were washed with water (2 x 10cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude compound was purified by silica gel chromatography (ethyl acetate/petroleum ether 10:1) to afford the title compound **(130)** (384 mg, 38 %). δ_H (250 MHz; $CDCl_3$) 0.97 (3H, m, C-(4)-H), 1.11 (6H, t, *J* 6.8, OCH_2CH_3), 1.43 (4H, m, C(1)-H & C(2)-H_2), 3.47 (1H, m, C(3)-H), 3.95 (4H, m, OCH_2CH_3), 4.43 (2H, s, $ArCH_2$), 7.33 (5H, m, ArH); δ_C (63 MHz; $CDCl_3$) 12.44 (d, J_{CP} 137.3, C-1), 16.03 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 20.98 (C-4), 21.25 (d, $^2J_{CP}$ 4.8, C-2,), 62.31 (d, $^2J_{CP}$ 5.9, OCH_2CH_3), 65.79 ($^3J_{CP}$ 6.4, C-3), 77.39 (CH_2Ph), 127.84, 128.12, 128.55, 137.27 (6C, Ar).

6.2.18. Diethyl 3-(Benzyloxy)cyclobutane-1-phosphonate (132)

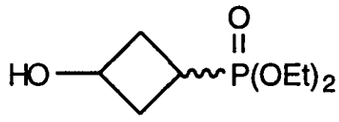


(132)

Diethyl methanephosphonate (5 g, 32.9 mmol) in a solution of anhydrous THF (150 cm^3) at -78 °C under an atmosphere of nitrogen was treated with *n*-butyllithium (13.2 cm^3, 33 mmol). The solution was stirred at -78 °C for 30 min and then 1-chloro-2-benxyloxy-3-bromopropane (4.3 g, 16.45 mmol) was added. The reaction mixture was stired at -78 °C for 1 h and then warmed to room temperature and stirred for a further 1 h. The reaction was quenched by the addition of saturated ammonium chloride solution. The THF was removed *in vacuo* and the aqueous layer extracted with dichloromethane (4 x 40 cm^3). The organic fractions were combined washed with water (2 x 40 cm^3) and brine (2 x 30 cm^3), dried over anhydrous $MgSO_4$, filtered and the

solvent removed under reduced pressure. The excess diethyl methanephosphonate (40 °C, 0.1 mmHg), unreacted 1-chloro-2-benxyloxy-3-bromopropane (100 °C, 0.1 mmHg) and some mono-substituted product (120-135 °C, 0.1 mmHg) are removed by distillation under reduced pressure. The residue was purified by Kugelrohr distillation (200-205 °C, 0.1 mmHg) to yield the desired products as a colourless oil **(132)** (2.4 g, 49 % yield) as a mixture of *E*- and *Z*-isomers in a 2:1 ratio. δ_H (250 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.3, OCH_2CH_3,), 2.84-3.83 (4H, br. m, C(2)-H & C(4)-H), 4.11 (4.7H, m, OCH_2CH_3 and C(3)-H of *E*-isomer), 4.25 (0.3H, m, C(3)-H of Z-isomer), 4.35 (2H, br. s, $PhCH_2O$), 7.33 (5H, br s, ArH); δ_C (63 MHz; $CDCl_3$) 16.41 (d, $^3J_{CP}$ 5.9, 2 x OCH_2CH_3), 20.9 (d, J_{CP} 154.5, C-1 *E*-isomer), 22.6 (d, J_{CP} 149.6, C-1 Z-isomer), 30.67 (d, $^2J_{CP}$ 5.9, C-2 Z-isomer), 31.68 (d, $^2J_{CP}$ 4.9, C-2 *E*-isomer), 61.57 (d, $^2J_{CP}$ 7.9, 2 x OCH_2CH_3), 69.81 ($PhOCH_2$), 70.13 (d, C-3 *E*-isomer, $^3J_{CP}$ 35.4), 71.37 (d, C-3 Z-isomer, $^3J_{CP}$ 4.9), 127.57, 127.68, 128.27, 137.79 (6C, Ar); δ_P (162 MHz; $CDCl_3$) 33.17 (*E*-isomer), 36.59 (Z-isomer); (NH_3 CI) *m/z* 299 ($[M+H]^+$, 40 %), 209 (13), 192 (12), 163 (10), 91 (100), 79 (20);*m/z* calc'd for $C_{16}H_{23}O_4P$ [M+H]: 299.1408, found 299.1410.

6.2.19. Diethyl 3-Hydroxycyclobutane-1-phosphonate (133)

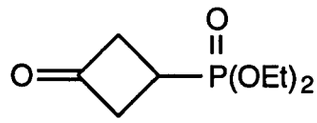


(133)

A solution of diethyl 3-(benzyloxy)cyclobutanephosphonate **(132)** (20g, 67.1 mmol) in methanol (150 cm^3) hydrogenated (3 atmospheres) over palladium on carbon (200 mg) until the uptake of hydrogen ceased (approximately 3 h). The catalyst was removed by filtration through celite which was washed with methanol (3 x 20 cm^3). Removal of the solvent *in vacuo* yielded the alcohols **(133)** as a colourless oil (13.9 g, 100 % yield), which

were used without further purification. ϑ_{max}/cm^{-1} (neat) 3382, 2995, 2910, 1445, 1235, 1163; δ_H (250 MHz; $CDCl_3$) 1.25 (6H, m, OCH_2CH_3), 1.9-2.55 (5H, m, (C(1)-H, C(2)-H & C(4)-H), 4.05 (4H, m, OCH_2CH_3), 4.25 (0.7H, m, C(3)-H *E*-isomer), 4.45 (0.3H, m, C(3)-H *Z*-isomer); δ_C (63 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 5.6, 2 x OCH_2CH_3), 19.14 (d, J_{CP} 154, C-1 *E*-isomer), 20.71 (d, J_{CP} 151, C-1 *Z*-isomer), 33.35 ($^2J_{CP}$ 6.2, C-2 & C-4 *Z*-isomer), 34.26 ($^2J_{CP}$ 5.3, C-2 & C-4 *E*-isomer), 61.61 (d, $^3J_{CP}$ 5.4, 2 x OCH_2CH_3), 64.28 (d, $^3J_{CP}$ 33, C-3 *E*-isomer), 65.00 (d, $^3J_{CP}$ 5.6, C-3 *Z*-isomer); δ_P (162 MHz; $CDCl_3$) 32.2 (*E*-isomer), 35.0 (Z-isomer); (EI) *m/z* 208 (M^+, 10 %), 195 (10), 165 (25), 138 (45), 109 (60), 91 (30), 83 (100);*m/z* calc'd for $C_8H_{18}O_4P$ [M+H]: 209.0940, found 209.0942.

6.2.20. Diethyl 3-Oxocyclobutane-1-phosphonate (134)

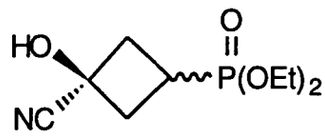


(134)

To a solution of $RuCl_3$ (150 mg) in dichloromethane (50 cm^3) was added a solution of $NaIO_4$ (2 g) in water (50 cm^3). The biphasic mixture was stirred at room temperature for 12 h. The aqueous layer as separated and extracted with dichloromethane (2 x 10 cm^3). The combined yellow organic layers were added to a solution of diethyl 3-hydroxycyclobutane-phosphonate **(133)** (12 g, 57.7 mmol) in dichloromethane (20 cm^3) and a solution of $NaIO_4$ (24.7 g, 115.4 mmol) in water (100 cm^3). The biphasic mixture was stirred vigourously (approximately 16 h) until the yellow colour persisted on standing. Sufficient water to dissolve the $NaIO_3$ was added to the reaction mixture. The two layers were separated and the aqueous layer extracted with dichloromethane (3 x 30 cm^3). The combined organic layers were washed with water (2 x 50 cm^3) and brine (2 x 40 cm^3), dried over anhydrous magnesium

sulfate, filtered and the solvent evaporated *in vacuo*. The crude ketone containing $RuCl_3$ was purified by Kugelrohr distillation (160-165 °C, 0.1 mmHg) to yield the pure ketone (10.8 g, 90 %). ϑ_{max}/cm^{-1} (neat) 2985, 1785, 1228, 1054; δ_H (250 MHz; $CDCl_3$) 1.21 (6H, t, *J* 7.3, OCH_2CH_3), 2.55 (1H, m, C(1)-H), 3.11-3.37 (4H, m, C(2)-H & C(4)-H), 4.01 (4H, q, *J* 7.3 OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 5.6, OCH_2CH_3), 20.47 (d, J_{CP} 157.9, C-1,), 49.15 (d, $^2J_{CP}$ 4.6, C-2 & C-4), 62.13 (d, $^2J_{CP}$ 6.6, OCH_2CH_3), 202.8 (d, $^3J_{CP}$ 18.4, C=O); δ_P (162 MHz; $CDCl_3$) 30.2; (NH_3 CI) *m/z* 224 ($[M+18]^+$, 22 %), 206 ($[M+H]^+$, 100), 178 (32), 165 (43), 138 (25), 109 (29);*m/z* calc'd for $C_8H_{16}O_4P$ [M+H]: 207.0784, found 207.0789.

6.2.21. *E/Z*-Diethyl 3-Cyano-3-hydroxycyclobutane-1-phosphonate (136)

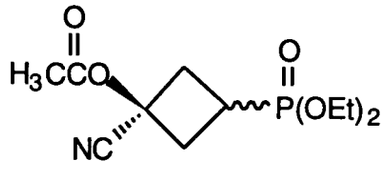


(136)

Ammonium chloride (1.09g, 20 mmol), sodium cyanide (1 g, 20 mmol) and alumina (2.8 g, 34 mmol) were suspended in acetonitrile (60 cm^3). The suspension was sonicated for 10 min and then a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (3.5 g, 17 mmol) in acetonitrile (5 cm^3) was added and the reaction was sonicated for 15 h. The reaction mixture was filtered through a pad of celite which was washed with acetonitrile (50 cm^3). The combined acetonitrile fractions were evaporated *in vacuo* and then taken up in dichloromethane (40 cm^3) and washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to yield a colourless oil which was identified as a mixture of the two isomers of diethyl 3-cyano-3-

hydroxycyclobutanephosphonate **(136)** (3.14g, 79 %). ϑ_{max}/cm^{-1} (neat) 3382, 2221, 1164, 1052, 1023; δ_H (250 MHz; $CDCl_3$) 1.24 (6H, t, *J* 7.2, OCH_2CH_3), 2.39-2.89 (5H, br. m, C(1)-H, C(2)-H & C(4)-H), 4.08 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$=5.6, 2 x OCH_2CH_3), 21.61 (d, J_{CP} 158.6, C-1 minor isomer), 24.74 (d, J_{CP} 156.1, C-1 major isomer), 36.23 (d, $^2J_{CP}$ 5.7, C-2 & C-4 minor isomer), 37.56 (d, $^2J_{CP}$ 4.9, C-2 & C-4 major isomer), 62.28 (d, $^2J_{CP}$ 6.7, 2x OCH_2CH_3), 63.26 (d, $^3J_{CP}$ 23.5, C-3 minor isomer), 64.35 (d, $^3J_{CP}$ 33.7 C-3 major isomer), 121.71 (CN); (NH_3 CI) *m/z* 233 ($[M+H]^+$, 16 %), 205 (83), 165 (81), 138 (100), 111 (69).

6.2.22. *E/Z*-Diethyl 3-(Acetoxy)-3-cyanocyclobutane-1-phosphonate (137)

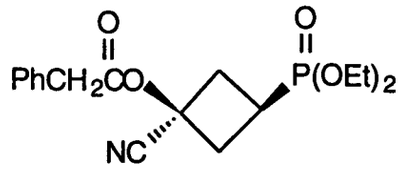


(137)

A solution of the semi-pure cyanohydrin **(136)** (100 mg, 0.43-mmol) and acetyl chloride (100 mg, 1 mmol) in dry pyridine (5 cm^3) was stirred at room temperature for 13 h. The reaction mixture was poured in to water (10 cm^3) and extracted with dicloromethane (3 x 10 cm^3). The combined organic extracts were washed with dilute hydrochloric acid (2 x 10 cm^3), saturated sodium bicarbonate solution (2 x 10 cm^3), water (2 x 10 cm^3) and brine (2 x 10 cm^3), dried over anyhydrous magnesium sulfate, filtered and the solvent removed in vacuo. The crude compound was purified by silica gel chromatography (dichloromethane/methanol 95:5) to afford the title compound **(137)** as a mixture of the two isomers in a 2:1 ratio (96 mg, 81 %) ϑmax/cm-1 (neat) 2986, 2223, 1757, 1216, 1025; δH (250 MHz; $CDCl_3$) 1.31 (6H, m, OCH_2CH_3), 2.03 (~1H, s, $C(O)CH_3$ major isomer), 2.13 (~2H, s, $C(O)CH_3$ minor isomer), 2.51-3.02 (5H, br m, C(1)-H, C(2)-H & C(4)-H), 4.09 (m, 4H, OCH_2CH_3); δC (63 MHz; $CDCl_3$) 16.22 (d, $^3J_{CP}$ 5.8, 2 x OCH_2CH_3), 20.17

($C(O)CH_3$ minor isomer), 20.34 ($C(O)CH_3$ major isomer), 23.48 (d, J_{CP} 158.7, C-1 major isomer), 25.03 (d, J_{CP} 156.5, C-1 minor isomer), 35.19 (d, $^2J_{CP}$ 6.0, C-2 minor isomer), 35.27 (d, $^2J_{CP}$ 5.2, C2 major isomer), 61.95 (d, $^2J_{CP}$ 5.8, 2 x OCH_2CH_3), 62.11 (d, $^3J_{CP}$ 34.2, C-3 minor isomer), 66.33 (d, $^3J_{CP}$ 20.1, C-3 major isomer), 117.26 (CN), 117.92 (CN), 168.33 (C=O), 168.52 (C=O); δP (162 MHz; $CDCl_3$) 27.7 (major isomer), 28.3 (minor isomer); (NH_3 CI) m/z 293 ($[M+18]^+$, 15 %), 276 ([M+H]+, 100), 234 (10), 205 (10), 165 (17), 138 (18).

6.2.23. *Z*-Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutane-1-phosphonate (138a)



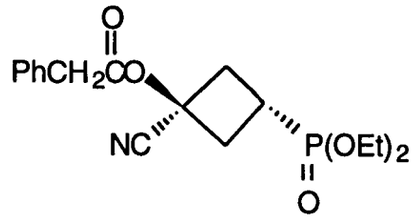
(138a)

To a solution of the crude cyanohydrin **(136)** (3.0 g, 12.9 mmol) in dichloromethane (40 cm^3) at 0 °C was added triethylamine (2.73 g, 27 mmol), and phenylacetyl chloride (2.1g, 13.4 mmol). The reaction mixture was stirred at room temperature for 12 h, after which time the solution was diluted to 100 cm^3 with dichloromethane and washed with water (3 x 20cm^3), dilute hydrochloric acid (2 x 20 cm^3), saturated sodium bicarbonate solution (3 x 20cm^3), water (2 x 20 cm^3) and brine (2 x 20 cm^3). The organic solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to yield the crude product as an orange oil. Separation of the isomers was achieved using silica gel chromatography (dichloromethane/methanol, 99:1) to give each isomer as a colourless oil. The isomer with the higher R_f value was crystalised by cooling an ethereal solution of the compound to -100 °C to give an off white solid **(138a)** (2.4 g, 54 %). R_f 0.65 (99:1 dichloromethane/methanol) m.p. 43 °C (Found C, 57.76; H, 6.28; N, 3.89; $C_{17}H_{23}NO_5P$ requires C, 58.10; H, 6.32; N, 3.99 %); ϑ_{max}/cm^{-1} (CH_2Cl_2)

3075, 3068, 3039, 2140, 1752; δ_H (250 MHz; $CDCl_3$) 1.24 (6H, t, *J* 7.7, OCH_2CH_3), 2.55-2.71 (3H, m, C(1)-H, C(2)-H & C(4)-H), 2.85-2.95 (2H, m, C(2)-H' & C(4)-H'), 3.64 (2H, s, $PhCH_2CO$), 4.01 (4H, m, OCH_2CH_3), 7.21 7.32 (5H, m, ArH); δ_C (63 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 21.05 (d, J_{CP} 154.8, C-1), 35.48 (d, $^2J_{CP}$ 4.9, C-2), 40.33 ($PhCH_2$), 62.12 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 65.48 (d, $^3J_{CP}$ 20.95, C-3), 117.96 (CN), 127.41, 128.65, 129.06, 132.25 (6C, Ar), 169.18 (C=O); δ_P (162 MHz; $CDCl_3$) 27.62; (EI) *m/z* 351 (M^+, 27 %), 205 (46), 181 (31), 169 (40), 118 (96), 91 (50), 83 (100);

Xray Crystallography: Crystals were colourless plates of formula $C_{17}H_{22}NO_5P$ grown from a saturated solution of pentane/diethyl ether/toluene at ambient temperature; orthorhombic, space group Pcba, a 9.991(5), b 12.885(8), c 28.39(2) Å, α 90, β 90, γ 90 °, *U* 3655(4) $Å^3$, *Z* 8, D_c 1.277 mg/dm^3, Mo-Kα radiation (λ 0.71069 Å), μ(Mo-Kα) 0.84 mm^{-1}, *T* 220 K, *R* 0.0366 for 2405 unique reflections observed ($I/\sigma(I) \geq 2.0$) reflections.

6.2.24. *E*-Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutane-1-phosphonate (138b)

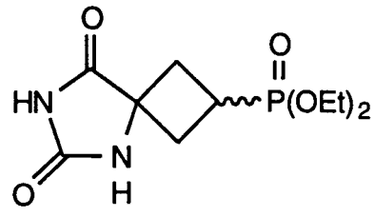


(138b)

The lower R_f isomer from above was isolated **(138b)** (1.3 g, 30 %). R_f 0.55 (99:1 dichloromethane/methanol) (Found C, 57.92; H, 6.38; N, 3.87; $C_{17}H_{22}NO_5P$ requires C, 58.10; H, 6.32; N, 3.99 %); ϑ_{max}/cm^{-1} (CH_2Cl_2) 2984, 2909, 1754, 2235; δ_H (250 MHz; $CDCl_3$) 1.30 (6H, t, OCH_2CH_3), 2.62 (3H, m, C(1)-H, C(2)-H & C(4)–H), 2.94 (2H, m, C(2)-H' & C(4)-H'), 3.63 (2H, s, $PhCH_2$), 4.07 (4H, m, OCH_2CH_3), 7.21-7.36 (5H, m, ArH); δ_C (63 MHz; $CDCl_3$) 16.27 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 23.76 (d, J_{CP} 155.5 C-1), 34.27 (d, $^2J_{CP}$ 4, C-2), 40.53

($PhCH_2$), 62.20 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 66.47 (d, $^3J_{CP}$ 12, C-3,), 117.13 (d, $^4J_{CP}$ 2.9 CN), 127.41, 128.48, 129.00, 132.31, (6C, Ar), 162.32 (C=O); δ_P (162 MHz; $CDCl_3$) 28.25; (EI) *m/z* 351 (M^+, 31 %), 205 (38), 181 (32), 169 (48), 118 (93), 91 (62), 83 (100).

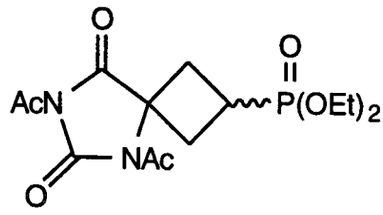
6.2.25. *E/Z*-Diethyl 3-Spirohydantoincyclobutane-1-phosphonate (139)



(139)

To a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (1 g, 4.88 mmol) in methanol (10 cm^3) and water (10 cm^3) adjusted to pH 7 (1M ammonium hydroxide solution) was added sodium cyanide (250 mg, 5.1 mmol) and "ammonium bicarbonate" (771 mg, 9.76 mmol). The reaction mixture was heated to reflux for 15 h, cooled and extracted with dichloromethane (2 x 10 cm^3) to remove any unreacted ketone. The aqueous layer was evaporated to dryness under reduced pressure. The crude compound **(139)** was used without further purification. δ_H (250 MHz; CD_3OD) 1.32 (6H, m, OCH_2CH_3), 2.5-3.6 (5H, br. m, C(1)-H, C(2)-H & C(4)-H_2), 4.26 (4H, m, OCH_2CH_3); δ_C (63 MHz; CD_3OD) 17.10 (d, $^3J_{CP}$ 6.9, 2 x OCH_2CH_3), 20.04 (d, J_{CP} 145, C-1 one isomer), 21.27 (d, J_{CP} 148, C-1 other isomer), 30.36 ($^2J_{CP}$ 5.8, C-2 & C-4 one isomer), 32.45 ($^3J_{CP}$ 5.8, C-2 & C-4 other isomer), 60.05 ($^3J_{CP}$ 14, C-3 one isomer), 64.29 ($^3J_{CP}$ 17, C-3 other isomer), 65.34 (d, $^3J_{CP}$ 5.9, 2 x OCH_2CH_3), 179.87 (2 x C=O), 180.77 (2 x C=O).

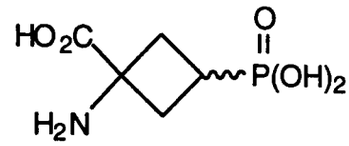
6.2.26. *E/Z*-Diethyl 3-(*N,N*-Diacetylspirohydantoin)cyclobutane-1-phosphonate (140)



(140)

To a solution of the crude spirohydantoin **(139)** (400 mg, 1.45 mmol) in dry pyridine (10 cm^3) was added acetyl chloride (0.25 cm^3). The reaction mixture was heated to reflux for 12 h, then poured into water (20 cm^3) and extracted with dichloromethane (3 x 10 cm^3). The organic extracts were washed with dilute hydrochloric acid (2 x 10 cm^3), saturated sodium bicarbonate solution (2 x 10 cm^3), water (2 x 15 cm^3) and brine (2 x 15 cm^3), then dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The crude oil was further purified by filtration through a small plug of silica (dichloromethane/methanol 19:1) to afford diethyl 3-(*N,N*-diacetylspirohydantoin)cyclobutanephosphonate **(140)** as an inseparable mixture of the two isomers (339 mg, 65 %). δ_H (250 MHz; $CDCl_3$) 1.08 (6H, m, OCH_2CH_3), 1.81 (s, ~2.4H, C(O)CH_3 major isomer), 1.95 (s, ~0.6H, C(O)CH_3 minor isomer), 1.98 (s, 3H, C(O)CH_3 both isomers), 2.45-2.76 (5H, m, C(1)-H, C(2)-H & C(4)-H), 3.99 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.13 (d, $^3J_{CP}$ 6.9, 2 x OCH_2CH_3), 20.02 (C(O)CH_3 major isomer), 20.12 (C(O)CH_3 minor isomer), 20.19 (C(O)CH_3 minor isomer), 20.22 (C(O)CH_3 major isomer), 20.35 (d, J_{CP} 149, C-1 one isomer), 21.58 (d, J_{CP} 153, C-1 other isomer), 30.02 ($^2J_{CP}$ 5.8, C-2 & C-4 one isomer), 32.35 ($^3J_{CP}$ 5.8, C-2 & C-4 other isomer), 60.85 ($^3J_{CP}$ 19, C-3 one isomer), 64.55 ($^3J_{CP}$ 23, C-3 other isomer), 62.34 (d, $^3J_{CP}$ 5.9, 2 x OCH_2CH_3), 178.66 (C=O), 179.87 (C=O), 179.99 (C=O), 180.77 (C=O).

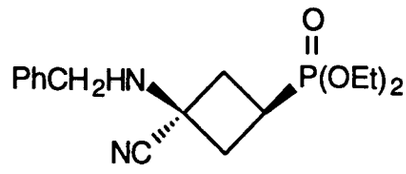
6.2.27. *E/Z*-3-Amino-3-carboxycyclobutane-1-phosphonic acid (78)



(78)

A solution of the crude spirohydantoin **(139)** (400 mg, 1.45 mmol) in sodium hydroxide solution (6 M, 10 cm^3) was heated to reflux for 24 h. The solution was cooled to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in water (3 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and eluted with aqueous pyridine (1M, 200 cm^3). Ninhydrin postive fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeated dissolution of the residue in water (5 cm^3) and re-evaporation (3 times) to afford an inseparable mixture of *E* - and *Z* - 3-amino-3-carboxycyclobutanephosphonic acids **(78)** (200 mg, 71 %). δ_H (250 MHz; $CDCl_3$) 2.27-2.61 (3H, m, C(1)-H, C(2)-H & C(4)-H), 2.73 (2H, m, C(2)-H' & C(4)-H'); δ_C (63 MHz; $CDCl_3$) 22.76 (d, J_{CP} 141, C-1 *E*-isomer), 25.10 (d, J_{CP} 142, C-1 *Z*-isomer), 31.65 (d, $^2J_{CP}$ 4.8, C-2 & C-4 *Z*-isomer), 31.77 (d, $^2J_{CP}$ 4.8, C-2 & C-4 *E*-isomer), 55.18 (d, $^3J_{CP}$ 16, C-3 *E*-isomer), 57.28 (d, $^3J_{CP}$ 14.5, C-3 *Z*-isomer), 176.40 (C=O *Z*-isomer), 175.22 (d, $^4J_{CP}$ 3.1, C=O *E*-isomer); δ_P (162 MHz; $CDCl_3$) 25.70 (*Z*-isomer), 26.51 (*E*-isomer).

6.2.28. Z-Diethyl 3-(Benzylamino)-3-cyanocyclobutane-1- phosphonate (141a)

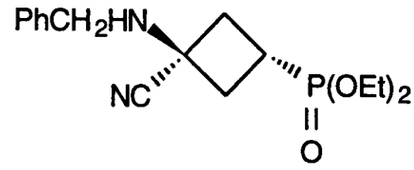


(141a)

To a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (2 g, 9.7 mmol) and sodium cyanide (480 mg, 9.8 mmol) in dry methanol was added benzylamine (1.2 g, 12.9 mmol). The solution was cooled to 0 °C and glacial acetic acid (1 cm^3) was added dropwise. The reaction mixture was heated gradually with stirring to 60 °C for 20 h. After cooling to room temperature the solution was neutralised with saturated sodium bicarbonate solution (5 cm^3), the solvent was removed under reduced pressure and the residue taken up in dichloromethane (30 cm^3) and water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 cm^3). The combined organic layers are washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* yielding the crude α-benzylaminonitrile as a mixture of the two isomers in a 3:2 ratio. The crude product was purified by silica gel chromatography (dichloromethane/methanol 95:5). Separation of the isomers was achieved by silica gel chromatography (3 times) (hexane/*iso*-propanol 8:2) to afford pure Z-Diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141a)** (1.4 g, 45 %). R_f 0.55 (8:2 hexane:*iso*-propanol) ϑ_{max}/cm^{-1} (CH_2Cl_2) 3274, 3033, 2985, 2953, 2222, 1605, 1496, 1455; δ_H (400 MHz; $CDCl_3$) 1.21 (6H, t, *J* 7.0, OCH_2CH_3), 1.97 (1H, br. s, NH), 2.31 (2H, m, C(2)-H & C(4)-H), 2.57 (3H, m, C(1)-H, C(2)-H' & C(4)-H'), 3.70 (2H, d, *J* 4.6, $PhCH_2$), 3.95 (4H, m, OCH_2CH_3), 7.18 (5H, m, Ar); δ_C (100 MHz; $CDCl_3$) 16.30 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 22.14 (d, J_{CP} 154.8, C-1), 34.85 (d, $^2J_{CP}$ 4.5, C-2 & C-4), 48.80 ($PhCH_2$), 52.50 (d, $^3J_{CP}$ 25.5,

C-3), 61.87 (d, $^2J_{CP}$ 4.5, OCH_2CH_3), 121.33 (CN), 127.31, 128.23, 128.32, 138.31 6C (Ar); δ_P (162 MHz; $CDCl_3$) 29.13; (NH_3 CI) m/z 323 ($[M+H]^+$, 5 %), 296 (100), 207 (11), 108 (22), 91 (62).

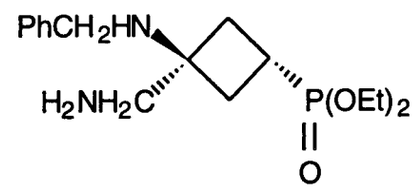
6.2.29. *E*-Diethyl 3-(Benzylamino)-3-cyanocyclobutane-1- phosphonate (141b)



(141b)

The lower R_f isomer from above was isolated **(141b)** (930 mg, 30 %). R_f 0.45 (85:15 hexane:*iso*-propanol) ϑ_{max}/cm^{-1} (CH_2Cl_2) 3272, 3033, 2986, 2952, 2222, 1608, 1496, 1455; δ_H (400 MHz; $CDCl_3$) 1.26 (6H, t, *J* 7.0, OCH_2CH_3), 1.86 (1H, br. s, NH), 2.20 (2H, m, C(2)-H & C(4)-H), 2.65 (2H, m, C(2)-H' & C(4)-H'), 2.88 (1H, m, C(1)-H), 3.74 (2H, br. s, $PhCH_2$), 4.03 (4H, m, OCH_2CH_3), 7.21 (5H, m, Ar); δ_C (100 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 24.54 (d, J_{CP} 154.8, C-1), 33.12 (d, $^2J_{CP}$ 6.4, C-2 & C-4), 48.86 ($PhCH_2$), 50.63 (d, $^3J_{CP}$ 25.5, C-3), 61.85 (d, $^2J_{CP}$ 6.4, OCH_2CH_3), 120.16 (d, $^4J_{CP}$ 4.8, CN), 127.36, 128.13, 128.41, 138.38 6C (Ar); δ_P (162 MHz; $CDCl_3$) 29.50; (NH_3 CI) m/z 323 ($[M+H]^+$, 7 %), 296 (100), 207 (17), 108 (20), 91 (54).

6.2.30. *E*-Diethyl 3-(Benzylamino)-3-(aminomethyl)cyclobutane-phosphonate (143)

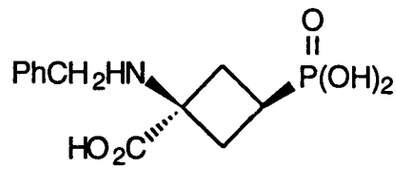


(143)

A solution of *E*-diethyl 3-(benzylamino)-3-cyanocyclobutane-phosphonate **(141b)** (50 mg, 1.5mmol) in methanol (20 cm^3) containing 3 drops

of concentrated hydrochloric acid, was hydrogenated over 10 % palladium on carbon (100 mg) at room temperature and 3 atmospheres for 12 h. The catalyst was removed by filtration through a pad of celite, which was washed with methanol (30 cm^3). The solvent was removed under reduced pressure to afford a pale yellow oil which was identified as *E*-diethyl 3-(benzylamino)-3-(aminomethyl)cyclobutanephosphonate **(143)** (42 mg, 86 %). δ_H (250 MHz; $CDCl_3$) 1.14 (6H, m, OCH_2CH_3), 1.87 (2H, br. s, CH_2NH_2), 2.03 (4H, m, C(1)-H, C(2)-H, C(3)-H & NH), 2.52 (2H, m, C(2)-H' & C(3)-H'), 3.93 (4H, m, OCH_2CH_3), 6.34 (2H, br. s, NH_2), 7.05 (5H, m, Ar); δ_C (63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 20.68 (d, J_{CP} 150.6, C-1), 30.38 (d, $^2J_{CP}$ 5.9, C-2), 44.29 ($PhCH_2$), 45.95 (d, $^4J_{CP}$ 3.4, CH_2NH_2), 61.66 (d, $^2J_{CP}$ 5.8, OCH_2CH_3), 126.83, 127.98, 128.23, 139.96 (6C, Ar); (NH_3 CI) *m/z* 327 ($[M+H]^+$, 8 %), 300 (16), 273 (24), 190 (100), 91 (32), 77 (13).

6.2.31. Z-3-(Benzylamino)-3-carboxycyclobutanephosphonic Acid (144a)

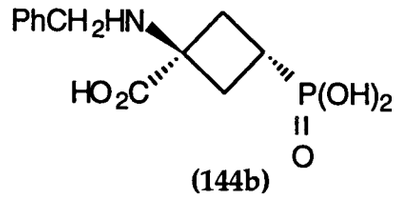


(144a)

Z-Diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141a)** (100 mg, 0.31mmol) was dissolved in hydrochloric acid (6M, 5cm^3). The solution was heated to reflux for 24 h, cooled to room temperature and the solvent removed *in vacuo*. Any residual hydrochloric acid was removed by the repeated addition of water (3 x 10 cm^3) and re-evaporation. The residue was dissolved in ethanol (5 cm^3) and propane oxide (1 cm^3) was added. The mixture was heated to reflux for 30 min, cooled and evaporated to dryness under reduced pressure to afford Z-(benzylamino)-3-carboxycyclobutanephosphonic acid **(144a)** as an off white solid (81 mg, 92 %)

δ_H (250 MHz; $CDCl_3$) 2.42 (2H, m, C(2)-H & C(4)-H), 2.92 (3H, m, C(1)-H & C(2)-H', C(4)-H'), 3.83 (2H, br. s, PhCH_2), 4.87 (1H, br. s, NH), 7.12 (5H, s, Ar); δ_C (63 MHz; $CDCl_3$) 17.88 (d, J_{CP} 155.5, C-1), 43.76 ($PhCH_2$), 49.22 (d, $^2J_{CP}$ 3.0, C-2 & C-4), 64.47 (d, $^3J_{CP}$ 6.9), 127.66, 129.53, 129.84, 133.10 (6C, Ar), 176.48 (C=O); (NH_3 CI) *m/z* 213 ($[M+18]^+$, 34 %), 196 ($[M+H]^+$, 18), 152 (100), 91 (45), 77 (22).

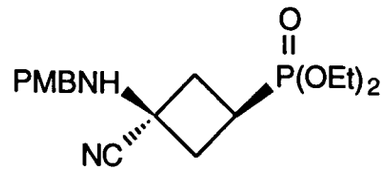
6.2.32. *E*-3-(Benzylamino)-3-carboxycyclobutanephosphonic Acid (144b)



(144b)

E-Diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(141b)** (100 mg, 0.31mmol) was dissolved in hydrochloric acid (6M, 5cm^3). The solution was heated to reflux for 24 h, cooled to room temperature and the solvent removed *in vacuo*. Any residual hydrochloric acid was removed by the repeated addition of water (3 x 10 cm^3) and re-evaporation. The residue was dissolved in ethanol (5 cm^3) and propane oxide (1 cm^3) was added, the mixture was heated to reflux for 30 min, cooled and evaporated to dryness under reduced pressure to afford *E* -3-(benzylamino)-3-carboxycyclobutanephosphonic acid **(144b)** as an off white solid (81 mg, 92 %) δ_H (250 MHz; $CDCl_3$) 2.55 (1H, m, C(1)-H), 2.87 (2H, m, C(2)-H & C(4)-H), 3.17 (2H, m, C(2)-H' & C(4)-H'), 3.94 (2H, br. s, PhCH_2), 4.83 (1H, s, NH), 7.24 (5H, s, Ar); δ_C (63 MHz; $CDCl_3$) 19.08 (d, J_{CP} 148.5, C-1), 43.63 ($PhCH_2$), 49.06 (d, $^2J_{CP}$ 3.2, C-2 & C-4), 61.65 (d, $^3J_{CP}$ 17.6, C-3), 127.36, 129.40, 129.84, 133.02 (6C, Ar), 171.25 (d, $^4J_{CP}$ 3.6, C=O); (NH_3 CI) *m/z* 213 ($[M+18]^+$, 26 %), 196 ($[M+H]^+$, 32), 152 (100), 91 (32), 77 (15).

6.2.33. *Z*-Diethyl 3-(*p*-Methoxybenzylamino)-3-cyanocyclobutane-phosphonate (145a)

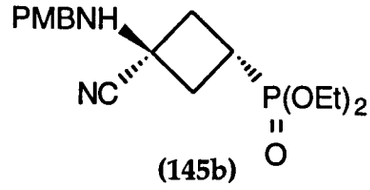


(145a)

To a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (1.5 g, 7.3 mmol) and sodium cyanide (430 mg, 8.74 mmol) in dry methanol was added *p*-methoxybenzylamine (1.2 g, 9.7 mmol). The solution was cooled to 0 °C and glacial acetic acid (1 cm^3) was added in a dropwise fashion. The reacton mixture was heated gradually with stirring to 60 °C for 20 h. After cooling to room temperature the solution was neutralised with saturated sodium bicarbonate solution (5 cm^3) and the solvent was removed under reduced pressure and the residue taken up in dichloromethane (30 cm^3) and water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 15 cm^3). The combined organic layers are washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* yielding the crude α-*p*-methoxybenzylaminonitrile as a mixture of the two isomers in a 3:2 ratio. The crude product was purified by silica gel chromatography (dichloromethane/methanol 95:5). Separation of the isomers was achieved by silica gel chromatography (3 times) (hexane/*iso*-propanol 85:15) to afford pure *Z*-Diethyl 3-(benzylamino)-3-cyanocyclobutanephosphonate **(145a)** (1.37 g, 53 %). R_f 0.52 (8:2 hexane:*iso*-propanol) (Found C, 57.82; H, 7.08; N, 7.85; $C_{17}H_{25}N_2O_4P$ requires C, 57.76; H, 7.13; N, 7.93 %); ϑ_{max}/cm^{-1} (CH_2Cl_2) 3278, 2982, 2839, 2221, 1795, 1686; δ_H (400 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.0, OCH_2CH_3), 2.06 (1H, br. s, NH), 2.32 (2H, m, C(2)-H & C(4)-H), 2.59 (3H, m, C(1)-H, C(2)-H' & C(4)-H'), 3.68 (2H, s, $PhCH_2$), 3.73 (3H, s, OCH_3), 4.00 (4H, m, OCH_2CH_3),

6.78 (2H, d, *J* 8.7, Ar), 7.20 (2H, d, *J* 8.7, Ar); δ_C (100 MHz; $CDCl_3$) 16.31 (d, $^3J_{CP}$ 4.8, OCH_2CH_3), 22.20 (d, J_{CP} 154.8, C-1), 34.87 (d, $^2J_{CP}$ 6.4, C-2 & C-4), 48.29 ($PhCH_2$), 52.44 (d, $^3J_{CP}$ 27.1, C-3), 55.10 (OCH_3), 61.92 (d, $^2J_{CP}$ 6.4, OCH_2CH_3), 113.73 (2C, Ar), 121.35 (CN), 129.50, 130.31, 158.85 (4C, Ar); δ_P (162 MHz; $CDCl_3$) 29.17; (NH_3 CI) *m/z* 354 ($[M+H]^+$, 5 %), 326 (71), 207 (20), 136 (12), 121 (100).

6.2.34. *E*-Diethyl 3-(*p*-Methoxybenzylamino)-3-cyanocyclobutane-phosphonate (145b)



(145b)

The lower R_f isomer from above was isolated **(145b)** (801 mg, 31 %). R_f 0.43 (85:15 hexane:*iso*-propanol) (Found C, 57.87; H, 7.19; N, 8.03; $C_{17}H_{25}N_2O_4P$ requires C, 57.76; H, 7.13; N, 7.93 %); ϑ_{max}/cm^{-1} (CH_2Cl_2) 3276, 2982, 2909, 2221, 1795, 1613, 1249, 1176; δ_H (400 MHz; $CDCl_3$) 1.33 (6H, t, *J* 7.0, OCH_2CH_3), 1.63 (1H, br. s, NH), 2.22 (2H, m, C(2)-H & C(4)-H), 2.68 (2H, m, C(2)-H' & C(4)-H'), 2.91 (1H, m, C(1)-H), 3.72 (2H, br. d, *J* 4.9, $PhCH_2$), 3.76 (3H, s, OCH_3), 4.07 (4H, m, OCH_2CH_3), 6.83 (2H, d, *J* 8.8, Ar), 7.23 (2H, d, *J* 8.8, Ar); δ_C (100 MHz; $CDCl_3$) 16.36 (d, $^3J_{CP}$ 4.8, OCH_2CH_3), 24.58 (d, J_{CP} 154.8, C-1), 33.12 (d, $^2J_{CP}$ 6.4, C-2 & C-4), 48.38 ($PhCH_2$), 50.60 (d, $^3J_{CP}$ 23.9, C-3), 55.13 (OCH_3), 61.89 (d, $^2J_{CP}$ 6.4, OCH_2CH_3), 113.84 (2C, Ar), 120.21 (d, $^4J_{CP}$ 4.8, CN), 129.96, 130.36, 158.92 (4C, Ar); δ_P (162 MHz; $CDCl_3$) 29.49; (NH_3 CI) *m/z* 352 ($[M+H]^+$, 6 %), 326 (28), 165 (13), 136 (22), 121 (100), 95 (11), 81 (12).

Xray Crystallography: Crystals were colourless plates of formula $C_{17}H_{22}NO_5P$ grown from a saturated solution of pentane/diethyl ether/toluene at ambient temperature; triclinic, space group P-1, a 7.630(3), b 9.882(5), c 13.604(6) Å, α 94.09(4), β 104.07(3), γ 99.27(4)°, *U* 975.4(8) $Å^3$, Z 2, D_c

1.200 mg/dm^3, Mo-Kα radiation (λ 0.71069 Å), μ(Mo-Kα) 0.84 mm^{-1}, *T* 220 K, *R* 0.0548 for 3443 unique reflections observed ($I/\sigma(I)\geq 2.0$) reflections.

6.2.35. Oxidative Removal of the *N*-*p*-Methoxybenzyl Group

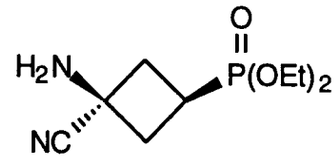
Ceric ammonium nitrate (822 mg, 1.5 mmol) was added to a solution of the *p*-methoxybenzylaminonitrile (80 mgs, 0.23 mmol) in acetonitrile and water (6 cm^3, 9:1). The reaction was monitored by tlc (dichlomethane/methanol 19:1). After 2 h no starting material remained. The reaction mixture was diluted by the addition of water (20 cm^3) and extracted with dichloromethane (3 x 15 cm^3). The organic extrracts were then extracted with dilute hydrochloric acid (1 M, 2 x 15 cm^3), the acidic fractions were adjusted to pH 8 and extracted with dichloromethane (3 x 10 cm^3). The dichloromethane fractions were washed with water (2 x 10 cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness to afford the deprotected α-aminonitrile compund as a crude oil which was used in the next step without further purification.

6.2.36. Removal of the *N*-*p*-Methoxybenzyl Group by Hydrogenation

A solution of the *p*-methoxybenzylaminonitrile (100 mgs, 0.29 mmol) in methanol (15 cm^3) was hydrogenated (3 atmospheres) over palladium on carbon for 4 h. The reaction mixture was filtered through a pad of celite which was washed with methanol (2 x 10 cm^3). The combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in a solution of dilute hydrochloric acid (1 M, 15 cm^3) and extracted with dichloromethane (2 x 10 cm^3). The aqueous fraction was adjusted to pH 8 with sodium hydroxide (1 M) and extracted with dichloromethane (3 x 15 cm^3). The dichloromethane fractions were washed with water (2 x 10 cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated to

dryness to afford diethyl 3-amino-3-cyanocyclobutanephosphonate as a crude oil which was used in the next step without further purification.

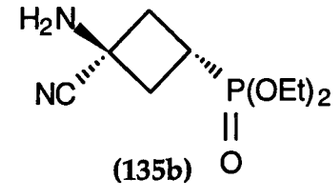
6.2.37. *Z*-Diethyl 3-Amino-3-cyanocyclobutanephosphonate (135a)



(135a)

Z-Diethyl3-(*p*-methoxybenzylamino)-3-cyanocyclobutanephosphonate **(145a)** was deprotected by either of the methods described above to afford Z-diethyl 3-amino-3-cyanocyclobutanephosphonate **(135a)**. δ_H (250 MHz; $CDCl_3$) 1.29 (6H, t, *J* 6.8, OCH_2CH_3), 2.16 (2H, br. s, NH_2), 2.24 (2H, m, C(2)-H & C(4)-H), 2.32 (3H, br. m, C(1)-H, C(2)-H' & C(4)-H'), 4.03 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 22.51 (d, J_{CP} 143, C-1), 34.25 (d, $^2J_{CP}$ 6.3, C-2 & C-4), 51.78 (d, $^3J_{CP}$ 24, C-3), 61.92 (d, $^2J_{CP}$ 6.5 OCH_2CH_3), 121.25 (CN).

6.2.38. *E*-Diethyl 3-Amino-3-cyanocyclobutanephosphonate (135b)

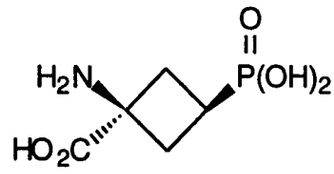


(135b)

E-Diethyl3-(*p*-methoxybenzylamino)-3-cyanocyclobutanephosphonate **(145b)** was deprotected by either of the methods described above to afford E-diethyl 3-amino-3-cyanocyclobutanephosphonate **(135b)**. δ_H (250 MHz; $CDCl_3$) 1.27 (6H, t, *J* 6.8, OCH_2CH_3), 2.18 (2H, br. s, NH_2), 2.35 (3H, m, C(1)-H, C(2)-H & C(4)-H), 2.68 (2H, m, C(2)-H' & C(4)-H'), 4.03 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 24.02 (d, J_{CP} 144, C-1), 32.85 (d, $^2J_{CP}$ 6.3,

C-2 & C-4), 50.01 (d, $^3J_{CP}$ 17, C-3), 61.82 (d, $^2J_{CP}$ 6.5 OCH_2CH_3), 120.06 (d, $^4J_{CP}$ 3.9, CN).

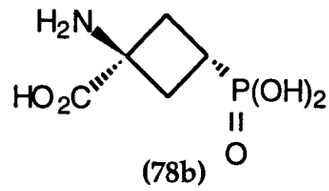
6.2.39. Z-3-Amino-3-carboxycyclobutanephosphonic Acid (78a)



(78a)

Crude Z-diethyl 3-amino-3-cyanocyclobutanephosphonate **(135a)** (100 mgs, 0.43 mmol) was dissolved in hydrochloric acid (6M, 10 cm^3) and the solution was heated to reflux for 48 h. After cooling the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (2 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and then eluted with aqueous pyridine (1 M, 200 cm^3). Ninhydrin active fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeatedly dissolving the the compound in water (10 cm^3) and re-evaporating (3-times) affording the title compound **(78a)** as an off white solid (62 mg, 74 %). δ_H (400 MHz; D_2O) 2.28 (2H, m, C(2)-H & C(4)-H), 2.56 (1H, m, C(1)-H), 2.73 (2H, M, C(2)-H' & C(4)-H'); δ_C (101 MHz; D_2O) 25.10 (d, J_{CP} 142, C-1), 31.65 (d, $^2J_{CP}$ 4.8, C-2 & C-4), 57.28 (d, $^3J_{CP}$ 14.5, C-3), 176.40 (C=O); δ_P (162 MHz; D_2O) 26.51; (FAB) *m/z* calc'd for $C_5H_{10}NO_5P$: 195.0296, found 195.0294.

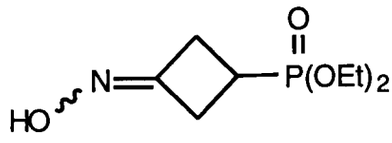
6.2.40. *E*-3-Amino-3-carboxycyclobutanephosphonic Acid (78b)



(78b)

Crude *E*-diethyl 3-amino-3-cyanocyclobutanephosphonate **(135b)** (100 mgs, 0.43 mmol) was dissolved in hydrochloric acid (6M, 10 cm^3) and the solution was heated to reflux for 48 h. After cooling the solution was evaporated to dryness under reduced pressure. The residue was dissolved in water (2 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and then eluted with aqueous pyridine (1 M, 200 cm^3). Ninhydrin active fractions were combined and evaporated to dryness under reduced pressure. Residual traces of pyridine were removed by repeatedly dissolving the the compound in water (10 cm^3) and re-evaporating (3 times) affording the title compound **(78b)** as an off white solid (67 mg, 76 %). δ_H (400 MHz; D_2O) 2.33 (3H, m, C(1)-H, C(2)-H & C(4)-H), 2.46 (2H, m, C(2)-H' & C(4)-H'); δ_C (101 MHz; D_2O) 22.76 (d, J_{CP} 141, C-1), 31.77 (d, $^2J_{CP}$ 4.8, C-2 & C-4), 55.18 (d, $^3J_{CP}$ 16, C-3), 175.22 (d, $^4J_{CP}$ 3.1, C=O); δ_P (162 MHz; D_2O) 25.70; (FAB) *m/z* calc'd for $C_5H_{10}NO_5P$: 195.0584, found 195.0581.

6.2.41. Diethyl 3-Oximinocyclobutanephosphonate (146)

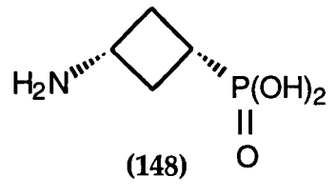


(146)

Hydroxylamine hydrochloride (520 mg, 8.1 mmol) was added to a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (500 mgs, 2.43 mmol) in water (10 cm^3) and the pH of the solution adjusted to 4 (1 M HCl). The

reaction mixture was heated to reflux for 15 h. After cooling the solution was adjusted to pH 8 (1 M NaOH) and extracted with dichloromethane (3 x 10 cm^3). The organic extracts were washed with water (2 x 10 cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to afford the title compound **(146)** (455 mg, 85 %). ϑ_{max}/cm^{-1} (neat) 3851, 3274, 2965, 2359, 1651; δ_H (250 MHz; $CDCl_3$) 1.18 (m, 6H, OCH_2CH_3), 1.75 (1H, s, *N*-OH), 2.25 (1H, m, C(1)-H), 2.97-3.30 (4H, m, C(2)-H & C(4)-H), 3.99 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.21 (d, $^3J_{CP}$ 5.9, OCH_2CH_3), 21.51 (d, J_{CP} 152.6, C-1), 31.91 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 32.76 (d, $^2J_{CP}$ 4.9, C-2 or C-4), 62.20 (d, $^2J_{CP}$ 5.9, OCH_2CH_3), 152.30 (d, $^3J_{CP}$ 15.8, C-3); (NH_3 CI) *m/z* 234 ($[M+H]^+$, 16 %), 217 (65), 206 (18), 191 (100), 165 (43).

6.2.42. *Z*-3-Aminocyclobutanephosphonic Acid (148)

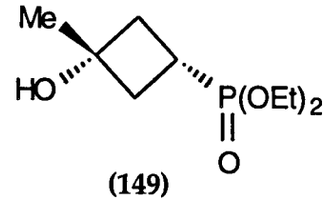


(148)

A solution of diethyl 3-oximinocyclobutanephosphonate **(146)** (400 mg, 1.81 mmol) in methanol (containing 4 drops of concentrated hydrochloric acid) was hydrogenated (3 atmospheres) over rhodium on alumina (30 mg) for 15 h. The reaction mixture was filtered through a pad of celite which was washed with methanol (3 x 10 cm^3). The combined filtrates were evaporated to dryness under reduced pressure. The residue was dissolved in water (3 cm^3) and applied to an ion exchange column (Dowex 50W, H^+ form). The column was washed with water (100 cm^3) and eluted with pyridine (200 cm^3). The ninhydrin positive fractions were combined and evaporated to dryness under reduced pressure, residual traces of pyridine were removed by repeated additon of water (5 cm^3) and re-evaporation (3 times) to afford the title compound **(148)** (169 mg, 62 %). δ_H (250 MHz; D_2O)

2.26 (2H, m, C(2)-H & C(4)-H), 2.49 (1H, m, C(1)-H), 2.63 (2H, m, C(2)-H' & C(4)-H'), 3.03 (1H, m, C(3)-H); δ_C (63 MHz; D_2O) 24.32 (d, J_{CP} 144, C-1), 28.41 (d, $^2J_{CP}$ 4.8, C-2 & C-4), 39.38 (d, $^3J_{CP}$ 4.8, C-3); δ_P (162 MHz; D_2O) 26.36; (NH_3 CI) *m/z* 169 ($[M+18]^+$, 24 %), 152 ($[M+H]^+$, 16), 135 (12), 118 (16), 107 (100).

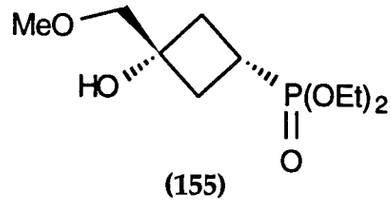
6.2.43. *Z*-Diethyl 3-Hydroxy-3-methylcyclobutanephosphonate (149)



(149)

A solution of diethyl 3-oxocyclobutanephosphonate **(134)** (100 mgs, 0.49 mmol) in anhydrous THF (15 cm^3) at -78 °C under an atmosphere of nitrogen, was treated with a solution of methyl magnesiumbromide (0.17 cm^3, 3 M in diethyl ether). The reaction mixture was stirred for 2 h at -78 °C then allowed to warm to room temperature and quenched with a saturated solution of ammonium chloride (15 cm^3). The THF was removed *in vacuo* and the aqueous residue was extracted with dichloromethane (3 x 15 cm^3). The combined organic fractions were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure to afford the title compound as a colouless oil **(149)** (88 mg, 81 %). δ_H (250 MHz; $CDCl_3$) 1.24 (6H, t, *J* 6.9, OCH_2CH_3), 1.33 (3H, s, CH_3), 2.20 (3H, m, C(1)-H, C(2)-H & C(4)-H), 2.68 (2H, m, C-(2)-H' & C(4)-H'), 4.01 (4H, m, OCH_2CH_3); δ_C (63 MHz; D_2O) 16.32 (d, $^3J_{CP}$ 6.9, OCH_2CH_3), 18.86 (d, J_{CP} 152, C-1), 26.36 (CH_3), 38.30 (d, $^2J_{CP}$ 4.9, C-2 & C-4), 61.82 (d, $^2J_{CP}$ 5.9, OCH_2CH_3), 70.27 (d, $^3J_{CP}$ 24.6, C-3); δ_P (101 MHz; $CDCl_3$) 32.15; (NH_3 CI) *m/z* 223 ($[M+H]^+$, 32 %), 205 (63), 177 (24), 149 (27), 122 (100), 107 (21);*m/z* calc'd for $C_9H_{20}O_4P$ [M+H]: 223.1096, found 223.1094.

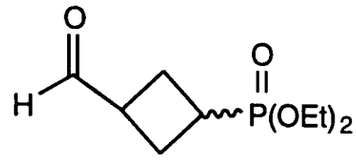
6.2.44. *Z*-Diethyl 3-Methoxymethyl-3-hydroxycyclobutanephosphonate (155)



(155)

A solution of methoxymethyltrimethylsilane (113 mgs, 0.97 mmol) in anhydrous anhydrous THF (10 cm^3) at -78 °C was treated with *sec*-butyllithium (0.75 cm^3, 1.3 M in cyclohexane). The solution was stirred for 30 min and then diethyl 3-oxocyclobutanephosphonate **(134)** (100 mgs, 0.49 mmol) in anhydrous THF (1 cm^3) was added. The reaction mixture was stirred at -78 °C for 1 h and then potassium hydride (23 mg, 0.58 mmol) was added and the solution warmed to room temperature. The reaction mixture was stirred at room temperature for 15 h and then quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed *in vacuo* and the aqueous solution extracted with dichloromethane (3 x 15 cm^3). The combined organic extracts were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate and evaporated to dryness to afford the title compound **(155)** (93 mg, 73 %). δ_H (250 MHz; $CDCl_3$) 1.24 (6H, t, *J* 7.8, $OCH_2\mathit{CH_3}$), 2.20 (2H, m, C(2)-H & C(4)-H), 2.52 (3H, m, C(1)-H, C(2)-H' & C(4)-H'), 3.32 (2H, s, $CH_3O\mathit{CH_2}$), 3.35 (3H, s, $\mathit{CH_3}OCH_2$), 4.01 (4H, m, $O\mathit{CH_2}CH_3$); δ_C (63 MHz; $CDCl_3$) 16.11 (d, $^3J_{CP}$ 6.9, $OCH_2\mathit{CH_2}$), 19.30 (d, J_{CP} 152, C-1), 33.99 (d, $^2J_{CP}$ 5.5, C-2 & C-4), 59.08 (s, $CH_3\mathit{OCH_2}$), 59.32 (s, $\mathit{CH_3}OCH_2$), 61.79 (d, $^2J_{CP}$ 5.9, $\mathit{OCH_2}CH_3$), 71.36 (d, $^3J_{CP}$ 24.3, C-3).

6.2.45. E/Z-Diethyl 3-Formylcyclobutanephosphonate (158)

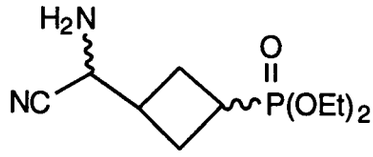


(158)

A solution of diethyl isonitrilemethylphosphonate (850 mg, 4.8 mmol) in anhydrous THF (25 cm^3) at -78 °C was treated with *n*-butyllithium (1.92 cm^3, 4.8 mmol). The solution was stirred at this temperature for 30 min and then a solution of diethyl 3-oxocyclobutanephosphonate **(134)** (900 mg, 4.4 mmol) in anhydrous THF (5 cm^3) was added. The reaction mixture was stirred for a further 2 h at -78 °C and then warmed to room temperature and quenched with water (5 cm^3). The THF was removed *in vacuo* and the residue redissolved in ether (20 cm^3) and hydrochloric acid (6 M, 10 cm^3). The biphasic solution was stirred at ambient temperature for 15 h. The ether was removed by evaporation under reduced pressure and the aqueous residue was extracted with dichloromethane (3 x 20 cm^3). The combined organic extracts were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure to afford a 1:1 mixture of the two diastereoisomers of the title compound **(158)** as a colourless oil (795 mg, 83 %) ϑ_{max}/cm^{-1} (neat) 2984, 2909, 2724, 1719, 1480, 1444, 1292, 1226; δ_H (250 MHz; $CDCl_3$) 1.14 (6H, m, OCH_2CH_3), 2.20-2.63 (5H, br. m, C(1)-H, C(2)-H & C(4)-H), 3.00 (1H, m, C(3)-H), 3.94 (4H, m, OCH_2CH_3), 9.54 (~0.5H, t, *J* 1.75, HC=O *Z*-isomer), 9.62 (~0.5H, d, *J* 1.2, HC=O *E*-isomer); δ_C (63 MHz; $CDCl_3$) 16.23 (d, $^3J_{CP}$ 5.9, 2 x OCH_2CH_3), 21.76 (d, $^2J_{CP}$ 5.9, C-2 & C-4 of one isomer), 22.41 (d, $^2J_{CP}$ 5.9, C-2 & C-4 of other isomer), 24.59 (d, J_{CP} 133, C-1 of one isomer), 24.59 (J_{CP} 151, C-1 of other isomer), 42.09 ($^3J_{CP}$ 17.7, C-3 of one isomer) 42.67 (d, $^3J_{CP}$ 11.8 of other isomer), 61.79 (d, $^2J_{CP}$ 5.9, 2 x OCH_2CH_3), 200.99 (d, $^4J_{CP}$ 2.9, C=O *Z*-isomer), 201.11 (C=O *E*-isomer); δ_P (162 MHz; $CDCl_3$) 29.99, 31.98; (NH_3 CI) *m/z* 221

([M+H]$^+$, 100 %), 191 (32), 165 (40), 152 (65), 138 (70), 109 (42), 55 (31);*m/z* calc'd for $C_9H_{17}O_4P$ [M+H]: 221.0940, found 221.0942.

6.2.46. (±)-E/Z-Diethyl 3-(Amino-cyanomethyl)cyclobutanephosphonate (159)

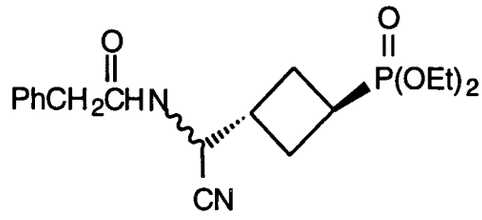


(159)

To a solution of the aldehyde **(158)** (400 mg, 1.8 mmol) in dry methanol (20 cm^3) was added sodium cyanide (135 mg, 2.7 mmol) and ammonium chloride (244 mg, 4.6 mmol). The reaction was stirred at ambient temperature with light excluded for 15 h. The methanol was removed under reduced pressure and the residue dissolved in dichloromethane (20 cm^3) and water (20 cm^3). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 20 cm^3). The combined organic layers were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield the title compound **(159)** as a pale orange oil which was used in the next step without any further purification (385 mg, 91 %). δ_H (250 MHz; $CDCl_3$) 1.21 (6H, m, OCH_2CH_3), 1.56 (2H, br. s, NH_2), 2.11-2.74 (6H, br. m, C(1)-H, C(2)-H, C(3)-H & C(4)-H), 3.61 (1H, m, *HC*(CN)NH_2), 3.99 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.36 ($^3J_{CP}$ 5.9, 2 x OCH_2CH_3), 23.79 (d, $^2J_{CP}$ 7.9, C-2 or C-4 of one isomer), 24.01 (d, J_{CP} 137, C-1 of one isomer), 24.09 (d, J_{CP} 149, C-1 of other isomer), 24.51 (d, $^2J_{CP}$ 5.9, C-2 or C-4 of one isomer & C-2 or C-4 of other isomer), 25.36 (d, $^2J_{CP}$ 5.9, C-2 or C-4 or other isomer), 36.37 (d, $^3J_{CP}$ 21.7, C-3 of one isomer), 36.39 (d, $^3J_{CP}$ 29, C-3 of other isomer), 47.55 (*C*(CN)NH_2,

E-isomer), 47.56 (d, $^4J_{CP}$ 3.2, C(CN)NH_2 Z-isomer), 61.64 (d, $^2J_{CP}$ 6.9, 2 x OCH_2CH_2), 120.62 (CN of one isomer), 120.67 (CN of other isomer); δ_P (250 MHz; $CDCl_3$) 30.52, 32.28.

6.2.47. (±)-*E*-Diethyl 3-(Phenylacetylamino)-cyanomethyl)cyclobutane-phosphonate (160a)

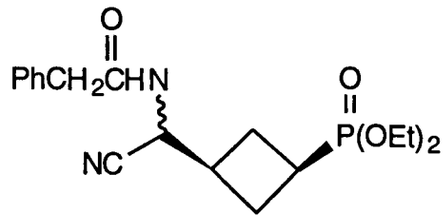


(160a)

Triethylamine (1.5 cm^3) was added dropwise to a solution of (±)-E/Z-diethyl 3-(amino-cyanomethyl)cyclobutanephosphonate **(159)** (360 mg, 1.46 mmol) and phenylacetyl chloride (250 mg, 1.6 mmol) in dry dichloromethane (20 cm^3) at room temperature. The reaction mixture was stirred for 15 h and then poured into water (20 cm^3). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 cm^3). The combine organic extracts were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to afford a crude product. The diastereoisomers were separated by silica gel chromatography to yield the title compound (214 mg, 80.5 %). R_f 0.48 (7:3 hexane:*iso*-propanol) (Found C, 59.29; H, 6.89; N, 7.69; $C_{18}H_{25}N_2O_4P$ requires C, 59.31; H, 6.92; N, 7.72 %); ϑ_{max}/cm^{-1} (neat) 3295, 2865, 2898, 2960, 2222, 1655, 1490, 1465, 1045; δ_H (400 MHz; $CDCl_3$) 1.26 (6H, dt, *J* 7.0 2.8, OCH_2CH_3), 1.96 (1H, br. s, NH), 2.04 (2H, m, C(2)-H & C(4)-H), 2.27 (2H, m, C(2)-H' & C(4)-H'), 2.49 (1H, m, C(1)-H), 2.79 (1H, m, C(3)-H), 3.57 (2H, s, $PhCH_2$), 4.00 (4H, m, OCH_2CH_3), 4.9 (1H, t, *J* 8.8, *HC*(CN)NHAcPh), 7.23 (3H, m, Ar), 7.29 (2H, m, Ar); δ_C (101 MHz; $CDCl_3$) 16.33 (d, $^3J_{CP}$ 6.4, OCH_2CH_3), 24.02 (d, J_{CP} 150, C-1), 24.10 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 24.30 (d, $^2J_{CP}$ 6.4, C-2 or C-4), 34.99 (d,

$^3J_{CP}$ 9.7, C-3), 42.78 ($PhCH_2$), 44.17 (*C*(CN)NHAcPh), 61.97 (d, $^2J_{CP}$ 4.8, OCH_2CH_3), 117.35 (CN), 127.31, 128.81, 128.96, 134.19 (6C, Ar), 170.94 (C=O); δ_P (162 MHz; $CDCl_3$) 32.42; (NH_3 CI) *m/z* 365 ($[M+H]^+$, 100 %), 338 (8), 273 (19), 165 (12), 136 (22), 91 (32).

6.2.48. (±)-Z-Diethyl 3-(Phenylacetylamino)-cyanomethyl)cyclobutane-phosphonate (160b)



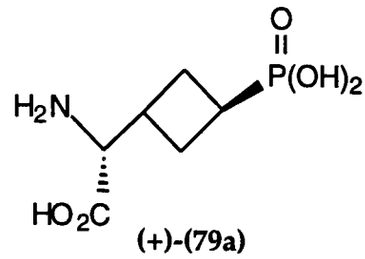
(160b)

The lower R_f isomer from above was isolated **(160b)** (228 mg, 86 %). R_f 0.40 (7:3 hexane:*iso*-propanol) (Found C, 59.28; H, 6.96; N, 7.77; $C_{18}H_{25}N_2O_4P$ requires C, 59.31; H, 6.92; N, 7.69 %); J_{max}/cm^{-1} () 3295, 2865, 2898, 2960, 2222, 1655, 1490, 1465, 1045; δ_H (400 MHz; $CDCl_3$) 1.28 (6H, dt, *J* 7.0 2.8, OCH_2CH_3), 2.06 (1H, br. s, NH), 2.11-2.46 (4H, br. m, C(2)-H & C(4)-H), 2.54 (1H, m, C(1)-H), 2.81 (1H, m, C(3)-H), 3.62 (2H, s, $PhCH_2$), 4.04 (4H, m, OCH_2CH_3), 4.78 (1H, dd, *J* 6.7 7.7, *HC*(CN)NHAcPh), 7.24 (3H, m, Ar), 7.29 (2H, m, Ar); δ_C (101 MHz; $CDCl_3$) 16.36 (d, $^3J_{CP}$ 6.4, OCH_2CH_2), 22.94 (d, $^2J_{CP}$ 6.5, C-2 or C-4), 23.19 (d, J_{CP} 148, C-1), 23.63 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 33.30 (d, $^3J_{CP}$ 17.7, C-3), 42.60 ($PhCH_2$), 43.55 (d, $^4J_{CP}$ 3.2, *C*(CN)NHAcPh), 62.07 (d, $^2J_{CP}$ 4.8, OCH_2CH_3), 117.29 (CN), 127.04, 128.61, 129.10, 134.32 (6C, Ar), 171.33 (C=O); δ_P (162 MHz; $CDCl_3$) 32.24; (NH_3 CI) *m/z* 365 ($[M+H]^+$, 100 %), 338 (11), 273 (22), 165 (17), 136 (34), 91 (37).

6.2.49. Enantioselective Enzyme Hydrolysis of (±)-*E*-Diethyl 3-(Phenylacetylamino)-cyanomethyl)cyclobutanephosphonate (±)-(160a)

(±)-*E*-Diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutanephosphonate **(±)-(160a)** (150 mg, 0.41 mmol) was dissolved in methanol (3 cm^3) and phosphate buffer (8 cm^3, 0.01 M, pH 7). Penicillinacylase immobilised on Eupergit (~20 units) was added. The reaction mixture was incubated at 27 °C and monitored by tlc (hexane/*iso*-propanol 7:3). After conversion had ceased (~6 h), the reaction mixture was filtered, adjusted to pH 4 (1 M HCl) and extracted with dichloromethane (3 x 10 cm^3). The combined organic fractions were washed with saturated sodium bicarbonate solution (2 x 10 cm^3), water (2 x 10 cm^3) and brine (2 x 10 cm^3) and dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield crude (-)-*E*-diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutanephosphonate **(-)-(160a)** (67 mg, 45 %). The acidic fraction from above was adjusted to pH 7 (1 M NaOH) and extracted with dichloromethane (3 x 10 cm^3). The combined organic fractions were washed with saturated sodium bicarbonate solution (2 x 10 cm^3), water (2 x 10 cm^3) and brine (2 x 10 cm^3) and dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield crude (+)-*E*-diethyl 3-(amino-cyanomethyl)cyclobutanephosphonate **(+)-(159a)** (42 mg, 41 %).

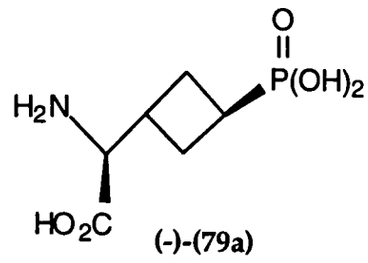
6.2.50. (+)-*E*-3-(Amino-carboxymethyl)cyclobutanephosphonic Acid (+)-(79a)



(+)-(79a)

(+)-*E*-diethyl 3-(amino-cyanomethyl)cyclobutanephosphonate **(+)-159a)** (35 mg, 0.14 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness. Residual traces of pyridine were removed by repeated dissolution in water and re-evaporation (3 times) to afford (+)-*E*-3-(amino-carboxymethyl)cyclobutanephosphonic acid **(+)-(79a)** (19 mg, 64 %) $[\alpha]_D^{20}$ +18.7° (*c* 0.8 in 1 M HCl), δ_H (400 MHz; D_2O) 2.09-2.27 (2H, br. m, C(2)-H & C(4)-H), 2.30-2.62 (3H, br. m, C(1)-H, C(2)-H' & C(4)-H'), 2.79 (1H, m, C(3)-H), 4.14 (1H, m, *CH*(NH_2)CO_2H); δ_C (101 MHz; D_2O) 22.45 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 22.62 (d, $^2J_{CP}$ 5.2, C-2 or C-4), 23.32 (d, J_{CP} 143, C-1), 33.28 (d, $^2J_{CP}$ 15.2, C-3), 49.29 (*C*(NH_2)CO_2H), 176.38 (C=O); δ_P (162 MHz; D_2O) 25.26; (FAB) *m/z* calc'd for $C_6H_{12}NO_5P$: 209.0452, found 209.0454.

6.2.51. (-)-*E*-3-(Amino-carboxymethyl)cyclobutanephosphonic Acid (-)-(79a)



(-)-(79a)

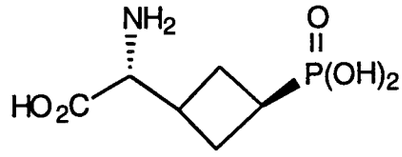
(-)-*E*-diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutane-phosphonate **(-)-(160a)** (67 mg, 0.18 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness. Residual traces of pyridine were removed by repeated dissolution in water and re-evaporation (3 times) to afford (-)-E-3-(amino-carboxymethyl)cyclobutanephosphonic acid **(-)-(79a)** (24-mg, 62 %) $[\alpha]_D^{20}$ -17.9° (*c* 0.8 in 1 M HCl), δ_H (400 MHz; D_2O) 2.09-2.27 (2H, m, C(2)-H & C(4)-H), 2.30-2.62 (3H, br. m, C(1)-H, C(2)-H' & C(4)-H'), 2.79 (1H, m, C(3)-H), 4.14 (1H, m, *CH*(NH_2)CO_2H); δ_C (101 MHz; D_2O) 22.45 (d, $^2J_{CP}$ 5.9, C-2 or C-4), 22.62 (d, $^2J_{CP}$ 5.2, C-2 or C-4), 23.32 (d, J_{CP} 143, C-1), 33.28 (d, $^2J_{CP}$ 15.2, C-3), 49.29 (*C*(NH_2)CO_2H), 176.38 (C=O); δ_P (162 MHz; D_2O) 25.26; (FAB) *m/z* calc'd for $C_6H_{12}NO_5P$: 209.0452, found 209.0454.

6.2.52. Enantioselective Enzyme Hydrolysis of (±)-Z-Diethyl 3-(Phenylacetylamino)-cyanomethyl)cyclobutanephosphonate (±)-160b)

(±)-Z-Diethyl 3-(phenylacetylamino)-cyanomethyl)cyclobutanephosphonate **(±)-160b)** (150 mg, 0.41 mmol) was dissolved in methanol (3 cm^3) and

phosphate buffer (8 cm^3, 0.01 M, pH 7). Penicillinacylase immobilised on Eupergit (~20 units) was added. The reaction mixture was incubated at 27 °C and monitored by tlc (hexane/*iso*-propanol 7:3). After conversion had ceased (~6 h), the reaction mixture was filtered, adjusted to pH 4 (1 M HCl) and extracted with dichloromethane (3 x 10 cm^3). The combined organic fractions were washed with saturated sodium bicarbonate solution (2 x 10 cm^3), water (2 x 10 cm^3) and brine (2 x 10 cm^3) and dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield crude (-)-Z-diethyl 3-(phenylacetylamino)-cyano-methyl)cyclobutanephosphonate **(-)-(160b)** (63 mg, 42 %). The acidic fraction from above was adjusted to pH 7 (1 M NaOH) and extracted with dichloromethane (3 x 10 cm^3). The combined organic fractions were washed with saturated sodium bicarbonate solution (2 x 10 cm^3), water (2-x 10 cm^3) and brine (2 x 10 cm^3) and dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to yield crude (+)-Z-diethyl 3-(amino-cyanomethyl)cyclobutanephosphonate **(+)-(159b)** (43 mg, 43 %).

6.2.53. (+)-Z-3-(Amino-carboxymethyl)cyclobutanephosphonic Acid (+)-(79b)

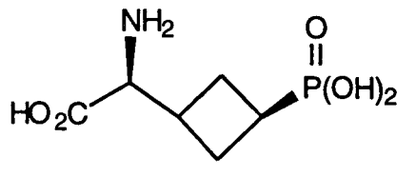


(+)-(79)

(+)-Z-diethyl 3-(amino-cyanomethyl)cyclobutanephosphonate **(+)-(159b)** (35 mg, 0.14 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness. Residual traces of

pyridine were removed by repeated dissolution in water and re-evaporation (3 times) to afford (+)-*Z*-3-(amino-carboxymethyl)cyclobutanephosphonic acid **(+)-(79b)** (18 mg, 61 %) $[\alpha]_D^{20}$ +13.6° (*c* 1 in 1 M HCl), δ_H (400 MHz; D_2O) 2.23-2.48 (4H, br. m, C(2)-H & C(4)-H), 2.55 (1H, m, C(1)-H), 2.87 (1H, m, C(3)-H), 4.21 (1H, *CH*(NH_2)CO_2H); δ_C (101 MHz; D_2O) 22.61 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 22.87 (d, $^2J_{CP}$ 4.2, C-2 or C-4), 25.15 (d, J_{CP} 142, C-1), 31.43 (d, $^3J_{CP}$ 13.8, C-3), 48.92 (d, $^4J_{CP}$ 2.8, *C*(NH_2)CO_2H), 176.21 (C=O); δ_P (162 MHz; D_2O) 26.48; (FAB) *m/z* calc'd for $C_6H_{12}NO_5P$: 209.0452, found 209.0453.

6.2.54. (-)-*Z*-3-(Amino-carboxymethyl)cyclobutanephosphonic Acid (-)-(79b);



(-)-(79b)

(-)-*Z*-diethyl 3-((phenylacetylamino)-cyanomethyl)cyclobutane-phosphonate **(-)-(160b)** (63 mg, 0.18 mmol) was dissolved in hydrochloric acid (6 M, 5 cm^3) and the reaction mixture heated to reflux for 36 h. After cooling the solvent was removed by evaporation under reduced pressure and the residue dissolved in water (1 cm^3), applied to an ion exchange column and washed with water (40 cm^3). The column was eluted with pyridine (1 M, 90 cm^3) and the ninhydrin active fractions were combined and evaporated to dryness, Residual traces of pyridine were removed by repeated dissolution in water and re-evaporation (3 times) to afford (-)-Z-3-(amino-carboxymethyl)cyclobutane-phosphonic acid **(-)-(79b)** (24 mg, 63 %) $[\alpha]_D^{20}$ -12.9° (*c* 0.9 in 1 M HCl), δ_H (400 MHz; D_2O) 2.23-2.48 (4H, br. m, C(2)-H & C(4)-H), 2.55 (1H, m, C(1)-H), 2.87 (1H, m, C(3)-H), 4.21 (1H, C(NH_2)CO_2H); δ_C (101 MHz; D_2O) 22.61 (d, $^2J_{CP}$ 4.8, C-2 or C-4), 22.87 (d, $^2J_{CP}$ 4.2, C-2 or C-4),

25.15 (d, J_{CP} 142, C-1), 31.43 (d, $^3J_{CP}$ 13.8, C-3), 48.92 (d, $^4J_{CP}$ 2.8, $C(NH_2)CO_2H$), 176.21 (C=O); δ_P (162 MHz; D_2O) 26.48; (FAB) *m/z* calc'd for $C_6H_{12}NO_5P$: 209.0452, found 209.0454.

6.2.55. Preparation of α-Methoxy-α-trifluoromethylphenylacetylamino Derivatives

General procedure: To a sample of diethyl 3-(amino-cyano-methyl)cyclobutanephosphonate (5 mg, 20 μmol) in dichloromethane (1 cm^3) was added triethylamine (50 μl) and α-methoxy-α-trifluoromethyl-phenylacetylchloride (240 μl of a 0.1 M solution in dichloromethane). The reaction mixture was stirred for 12 h at room temperature and then the solvent removed by evaporation under reduced pressure. The residue was dissolved in $CDCl_3$ and the sample analysed by ^{19}F nmr spectroscopy.

(±)-*E*-Diethyl 3-((α-methoxy-α-trifluoromethylphenylacetylamino)-carboxymethyl)cyclobutanephosphonate

δ_F (376 MHz; $CDCl_3$) -71.89 & -72.84

(+)-*E*-Diethyl 3-((α-Methoxy-α-trifluoromethylphenylacetylamino)-carboxymethyl)cyclobutanephosphonate

δ_F (376 MHz; $CDCl_3$) -71.89

(±)-*Z*-Diethyl 3-((α-Methoxy-α-trifluoromethylphenylacetylamino)-carboxymethyl)cyclobutanephosphonate

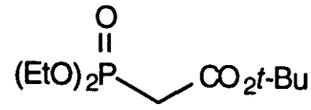
δ_F (376 MHz; $CDCl_3$) -69.85 & -71.91

(+)-*Z*-Diethyl 3-((α-Methoxy-α-trifluoromethylphenylacetylamino)-carboxymethyl)cyclobutanephosphonate

δ_F (376 MHz; $CDCl_3$) -71.91.

6.3. Synthesis of Cycloalkane 1,1-Bisphosphonic and 1-Carboxy-1-Phosphonic Acids

6.3.1. *t*-Butyl Diethyl phosphonoacetate (192)



(192)

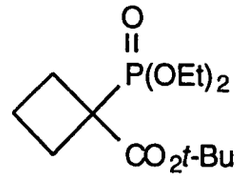
A solution of *t*-butyl bromoacetate (50 g, 0.26 mol) and triethyl phosphite (42.6 g, 0.26 mol) (freshly distilled from sodium) was heated gently (80 °C). The solution was heated further until the ethyl bromide began to distil (oil bath temperature 110 °C). After 30 min the reaction was cooled and the product distilled under reduced pressure to yield the desired compound (57 g, 87 %). (120-122 °C, 0.2 mmHg) (115 °C, 0.2 mmHg) (lit.,[8]) ϑ_{max}/cm^{-1} (neat) 2982, 1729, 1259, 1211, 1117, 1054, 1028; δ_H (250 MHz; $CDCl_3$) 1.37 (6H, t, *J* 7.3, OCH_2CH_3), 1.5 (9H, s, $C(CH_3)_3$), 3.9 (2H, d, J_{HCP} 22, PCH_2), 4.2 (4H, dq, *J* 7.3, 7.3, OCH_2CH_3); (NH_3 CI) *m/z* 253 ($[M+H]^+$, 10 %), 197 (91), 179 (100), 151 (72), 126 (64), 57 (84), 41 (31).

6.3.2. General Procedure for Preparation of Diethyl *t*-Butyl-1-carboxy-cycloalkanephosphonates (201-203)

A suspension of benzyltriethylammonium chloride (2.0 g, 8.7 mmol) in 50 % aqueous NaOH (20 cm^3) was treated with a solution of *t*-butyl diethylphosphonoacetate (2.0 g, 7.9 mmol) in the appropriate 1,ω-dibromoalkane (10 cm^3). The reaction mixture was stirred at room temperature for 24-48 h, poured into dichloromethane (150 cm^3), washed with water (7 x 100 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was distilled under reduced pressure (150 °C, 0.2 mmHg). Tlc (petroleum ether:ethanol, 97:3) indicated that the product was still impure.

The desired product was isolated by flash column chromatography on silica gel (petroleum ether:ethanol, 97:3).

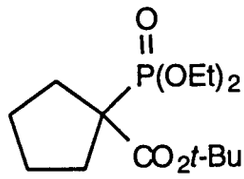
6.3.3. Diethyl *t*-Butyl 1-Carboxycyclobutanephosphonate (201)



(201)

Diethyl *t*-butyl 1-carboxycyclobutanephosphonate **(201)** was prepared as described above (970 mg, 42 %). ϑ_{max}/cm^{-1} (neat) 2981, 1724, 1285, 1055; δ_H (250 MHz; $CDCl_3$) 1.32 (t, 6H, *J* 7.8, OCH_2CH_3), 1.48 (9H, s, $C(CH_3)_3$), 2.00 (2H, m, C(3)-H), 2.62 (4H, m, (C(2)-H & C4-(H_2)), 4.16 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.27 (d, $^3J_{CP}$ 6, OCH_2CH_3), 17.14 (d, $^3J_{CP}$ 14.3, C-3), 27.5 (d, $^3J_{CP}$ 1.7, C(2) & C-4), 27.92 ($OC(CH_3)_3$), 46.27 (d, J_{CP} 137, C-1), 62.55 (d, $^2J_{CP}$ 16.5, OCH_2CH_3), 81.24 ($OC(CH_3)_3$), 171.01 (C=O); δ_P (101 MHz; $CDCl_3$) 25.2; (NH_3 CI) *m/z* 293 ($[M+H]^+$, 30 %), 254 (50), 237 (100).

6.3.4. Diethyl *t*-Butyl 1-Carboxycyclopentanephosphonate (202)

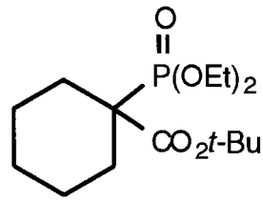


(202)

Diethyl *t*-butyl 1-carboxycyclopentanecphosphonate **(202)** was prepared as described above (1.57g, 65%). ϑ_{max}/cm^{-1} (neat) 2980, 2940, 1724, 1455, 1254, 1220, 1029; δ_H (250 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.1, OCH_2CH_3), 1.37 (9H, s, $C(CH_3)_3$), 1.55-1.75 (4H, br m, (C(3)-H & C(4)-H), 1.82-2.11 (2H, br m, (C(5)-H' & C(2)-H'), 2.21-2.39 (2H, br m, (C(5)-H' & C(2)-H'), 4.06 (4H, quint, *J* 7.1, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.24 (d, $^3J_{CP}$ 7, OCH_2CH_3), 25.03 (d, $^3J_{CP}$

11.8, C-3 & C-4), 27.84 ($OC(CH_3)_3$), 32.37 (C-2 & C-(5)), 53.83 (d, J_{CP} 135.2, C-1), 62.25 (d, $^2J_{CP}$ 16.9, OCH_2CH_3), 80.96 ($OC(CH_3)_3$), 170.79 (C=O); δ_P (101 MHz; $CDCl_3$) 28.0; (NH_3 CI) *m/z* 307 ($[M+H]^+$, 40 %), 268 (30), 251 (100), 206 (10).

6.3.5. Diethyl *t*-Butyl 1-Carboxycyclohexanephosphonate (203)



(203)

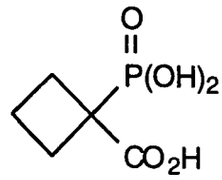
Diethyl *t*-butyl 1-carboxycyclohexanecphosphonate **(203)** was prepared as described above (1.72g, 43 %). ϑ_{max}/cm^{-1} (neat) 2990, 2940, 1730, 1455, 1250, 1210, 1060; δ_H (250 MHz; $CDCl_3$) 1.23 (6H, t, *J* 7.1, OCH_2CH_3), 1.37 (9H, s, $C(CH_3)_3$), 1.37-1.52 (2H, broad m, C(2)-H′ & C(6)-H′), 2.02-1.61 (6H, broad m, C(2)-H′, C(6)-H′, C(3)-H & C(5)-H), 2.30-2.21 (2H, broad m, C(4)-H), 4.16 (4H, quint, *J* 7.1, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.22 (d, $^3J_{CP}$ 4,6, OCH_2CH_3), 22.36 (d, $^3J_{CP}$ 11.8, C-3 & C-5), 25.15 (C-4), 27.66 ($C(CH_3)_3$), 29.49 (d, $^2J_{CP}$ 4.5, C(2) & C-6), 56.78 (d, J_{CP} 148.1, C-1), 62.23 (d, $^2J_{CP}$ 6.9, OCH_2CH_3), 80.86 ($OC(CH_3)_3$), 170.72 (C=O); δ_P (101 MHz; $CDCl_3$) 28.7; (NH_3 CI) *m/z* 332 ($[M+H]^+$, 45 %), 293 (25), 277 (100), 232 (15).

6.3.6. General Procedure for the Preparation of 1-Carboxycycloalkane-1-phosphonic Acids (207-209)

The diethyl *t*-butyl 1-carboxycycloalkanephosphonate **(201-203)** (500 mg, 1.7 mmol) was treated with an ice cold solution of trifluoroacetic acid (3 cm^3) for 1 h. The acid was removed *in vacuo*. Residual traces of acid were removed by the repeated addition and evaporation of water (3 x 3 cm^3). The crude residue was taken up in dichloromethane (4 cm^3) and treated with bromotrimethylsilane (2.2 cm^3, 17 mmol) for 48 h, lyophillised, shaken with

water and lyophillised again to yield the desired compounds **(207-209)**, which was converted to the dicyclohexylamine salts without further purification

6.3.7. 1-Carboxycyclobutanephosphonic Acid (207)



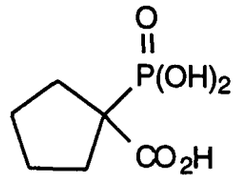
(207)

1-Carboxycyclobutanephosphonic acid **(207)** was prepared as described above (260 mg, 85 %). δ_H (250 MHz; D_2O) 2.06-1.95 (2H, m, C(3)-H), 2.63-2.54 (4H, m, C(2)-H & C(4)-H); δ_C (63 MHz; D_2O) 17.14 (d, $^3J_{CP}$ 14.3, C-3), 27.5 (C-2 & C-4), 46.2 (d, J_{CP} 137, C-1), 174 (C=O); δ_P (162 MHz; D_2O) 25.1; (NH_3 CI) *m/z* 181 ($[M+H]^+$, 35 %) 137 (100), 119 (32), 101 (13).

6.3.8. Dicyclohexylammmonium 1-Carboxycyclobutanephosphonic Acid (210)

1-Carboxycyclobutanephosphonic acid **(207)** (200 mg, 1.1 mmol) was treated with ethanol (4 cm^3) and dicyclohexylamine (283 mg, 1.1 mmol) to yield the crude title compound which was recrystalised from methanol/diethyl ether to give dicyclohexylammonium 1-carboxycyclobutanephosphonic acid **(210)** as a white crystalline solid (318 mg, 80 %). m.p. 230-233°C (Found C, 56.49; H, 8.85; N, 3.76; $C_{17}H_{32}NO_5P$ requires C, 56.47; H, 8.93; N, 3.88%).

6.3.9. 1-Carboxycyclopentanephosphonic Acid (208)



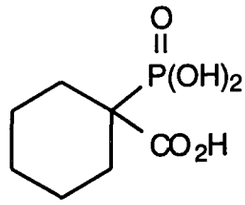
(208)

1-Carboxycyclopentanephosphonic acid **(208)** was prepared as described above (250 mg, 81 %). δ_H (250 MHz; D_2O) 1.52-1.75 (4H, m, C(3)-H_2 & C(4)-H_2), 1.82-2.15 (2H, m, (C(2)-H & C(5)-H), 2.24-2.31 (2H, m, (C(2)-H' & C(5)-H'); δ_C (63 MHz; D_2O) 25.03 (d, $^3J_{CP}$ 11.8, C(3) & C-4), 32.55 (C-2 & C-5), 53.91 (d, J_{CP} 132.8, C-1), 172.91 (C=O); δ_P (162 MHz; D_2O) 25.0; (NH_3 CI) *m/z* 195 ($[M+H]^+$, 55 %), 151 (100) 133 (14), 115 (16), 87 (31).

6.3.10. Dicyclohexylammonium 1-Carboxycyclopentanephosphonic Acid (211)

1-Carboxycyclopentanephosphonic acid **(208)** (200 mg, 1.0 mmol) was treated with ethanol (4 cm^3) and dicyclohexylamine (181 mg, 1.0 mmol). The crude compound was recrystallised from methanol/diethylether to yield the desired compound **(211)** as a white crystalline solid (326 mg, 87%). m.p. 224-226 °C (Found C, 57.74; H, 9.30; N, 3.84; $C_{18}H_{34}NO_5P$ requires C, 57.56; H, 9.23; N, 3.73 %).

6.3.11. 1-Carboxycyclohexanephosphonic Acid (209)



(209)

1-Carboxycyclohexanephosphonic acid **(209)** was prepared as described above (260 mg, 80 %). δ_H (250 MHz; D_2O) 1.24-1.40 (2H, m, C(2)-H'

& C(6)-H'), 1.64-1.87 (6H, m, C(2)-H', C(6)-H', C(3)-H, C(5)-H), 2.36-2.51 (2H, m, C(4)-H); δ_C (63 MHz; D_2O) 24.21 (d, $^3J_{CP}$ 12.6, C(3) & C-5), 26.86 (C-4), 31.58 (d, $^2J_{CP}$ 4.7, C(2) & C-6), 51.11 (d, J_{CP} 127.2, C-1); δ_P (162 MHz; D_2O) 25.1; (NH_3 CI) *m/z* 209 ([M+1]$^+$, 45 %), 161 (100) 143(14), 133 (10), .

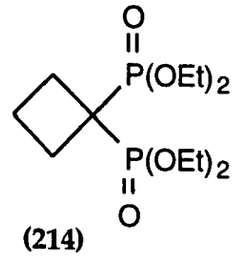
6.3.12. Dicyclohexylammonium 1-Carboxycyclohexanephosphonic Acid (212)

1-Carboxycyclohexanephosphonic acid **(209)** (200 mg, 0.96 mmol) was treated with ethanol (4 cm^3) and dicyclohexylamine (174 mg, 0.96 mmol). The crude compound was recrystalised from methanol/diethylether to yield the desired compound **(212)** as a white crystalline solid (336 mg, 90%). m.p. 250-254 °C (Found C, 58.69; H, 9.51; N, 3.69; $C_{19}H_{36}NO_5P$ (389.26) requires C, 58.57; H, 9.32; N, 3.60%).

6.3.13. General Procedure for Preparation of Tetraalkyl 1,1-cycloalkane-bisphosphonates (214-216)

A suspension of benzyltributylammonium chloride (1.78 g, 4.95 mmol) in 50 % aqueous NaOH (15 cm^3) was treated with a solution of the tetraalklmethylenebisphosphonate (1.15 g, 4.95 mmol) in the appropriate 1,ω-dibromoalkane (10 cm^3). The reaction mixture was stirred at room temperature for 48 h, poured into dichloromethane (150 cm^3), washed with water (7 x 100 cm^3) and brine (2 x 100 cm^3), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Tlc (petroleum ether:ethanol,93:7) indicated the presence of two products which were separated on silica gel by flash chromatography (petroleum ether:ethanol, 93:7) to yield the desired compound **(214-216)**.

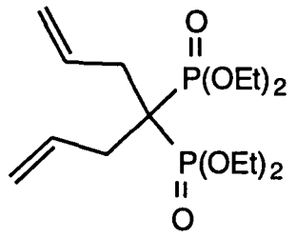
6.3.14. Tetraethyl 1,1-Cyclobutanebisphosphonate (214)



(214)

Tetraethyl 1,1-cyclobutanebisphosphonate **(214)** was prepared as described above (480 mg, 37 %). ϑ_{max}/cm^{-1} (neat) 2984, 2908, 1647, 1369, 1249, 1060; δ_H (250 MHz; $CDCl_3$) 1.23 (12H, t, *J* 7.3, OCH_2CH_3), 2.08 (2H, m, C(3)-H), 2.50 (4H, m, C(2)-H & C(4)-H), 4.12 (8H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.13 (OCH_2CH_3), 17.46 (t, $^3J_{CP}$ 6.0, C-3), 24.95 (t, $^2J_{CP}$ 6.1, C(2) & C-4), 37.7 (t, J_{CP} 140.7, C-1), 62.3 (OCH_2CH_3); δ_P (162 MHz; $CDCl_3$) 26.9; (EI) *m/z* 328 (M^+, 10%), 191 (100), 163 (20), 135 (30).

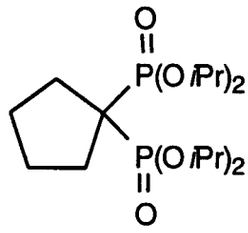
6.3.15. Tetraethyl Diprop-2-enemethanebisphosphonate (219)



(219)

A by-product from the above reaction was identified as tetraethyl diprop-2-enemethanebisphosphonate **(219)** (125 mg, 10 %). ϑ_{max}/cm^{-1} (neat) 4342, 3078, 2982, 2910, 1639, 1479, 1443, 1417, 1392, 1369, 1240; δ_H (250 MHz; $CDCl_3$) 1.23 (12H, m, OCH_2CH_3), 2.4-2.6 (4H, m, C(2)-H & C'(2)-H), 4.1 (8H, m OCH_2CH_3), 5.0 (4H, m, C(4)-H & C'(4)-H), 5.89 (2H, m, C(3)-H & C'(3)-H); δ_C (63 MHz; $CDCl_3$) 16.11 (OCH_2CH_3), 34.85 (t, $^2J_{CP}$ 4.7, C-2 & C'-2), 44.9 (t, J_{CP} 130.8, C-1), 62.2 (OCH_2CH_3), 117.81 (C-4 & C'-4), 133.14 (t, $^3J_{CP}$ 6.1, C-3 & C'-3); δ_P (162 MHz; $CDCl_3$) 26.3; (NH_3 CI) *m/z* 369 ($[M+H]^+$, 100 %), 232 (10), 215 (10), 183 (12).

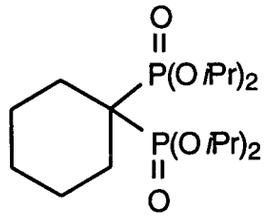
6.3.16. Tetra-*iso*-propyl 1,1-Cyclopentanebisphosphonate (215)



(215)

Tetra-*iso*-propyl 1,1-cyclopentanebisphosphonate **(215)** was prepared as described above (650 mg, 50 %). ϑ_{max}/cm^{-1} (neat) 2979, 1469, 1455, 1385, 1374, 1245, 1108, 990; δ_H (250 MHz; $CDCl_3$) 1.3 (12H, d, *J* 6.4, OCH(CH_3)$_2$), 1.47-1.55 (4H, m, C(3)-H & C(4)-H), 2.1 (4H, tt, *J* 20.3, 7.9, C(2)-H & C(5)-H), 4.61 (4H, m, OC*H*(CH_3)$_2$); δ_C (63 MHz; $CDCl_3$) 23.64 & 24.03 (OCH(CH_3)$_2$), 26.68 (t, $^3J_{CP}$ 4.2, C-3 & C-4), 31.35 (t, $^2J_{CP}$ 4.3, C(2) & C-5), 44.93 (t, J_{CP} 127.5, C-1), 70.5 (OCH(CH_3)$_2$); δ_P (101 MHz; $CDCl_3$) 27.2; (EI) *m/z* 398 (M^+, 16 %), 357 (15), 315 (11), 273 (22), 233 (88), 213 (60), 191 (33), 149 (100), 67 (61), 43 (81).

6.3.17. Tetra-*iso*-propyl 1,1-Cyclohexanebisphosphonate (216)



(216)

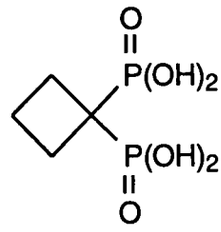
Tetra-*iso*-propyl 1,1-cyclohexanebisphosphonate **(216)** was prepared as described above (520 mg, 40 %) and some unreacted starting material. ϑ_{max}/cm^{-1} (neat) 2940, 1450, 1250, 1060; δ_H (250 MHz; $CDCl_3$) 1.26 (12H, d, *J* 6.4, OCH(CH_3)$_3$), 1.46 (2H, quint, *J* 6.1, C(4)-H), 1.72 (4H, quint, *J* 7.4, C(3)-H_2 & C(5)-H_2), 2.14-1.91 (4H, m, C(2)-H & C(6)-H), 4.61 (4H, m, OC*H*(CH_3)$_3$); δ_C (60 MHz; $CDCl_3$) 23.91 (OCH(CH_3)$_2$), 24.22 (OCH(CH_3)$_2$), 21.37 (t, $^3J_{CP}$ 6.5, C-3 & C-5), 24.84 (C-4), 26.93 ($^2J_{CP}$ 4.7, C(2) & C-6), 46.25 (t, J_{CP} C-1), 70.71

($OCH(CH_3)_2$); δ_P (162 MHz; $CDCl_3$) 28.1; (NH_3 CI) *m/z* 409 ($[M+H]^+$, 20 %), 371 (24), 329 (18), 287 (17), 247 (78), 207 (82), 163 (100), 67 (57), 43 (72).

6.3.18. General Procedure for the Preparation of Cycloalkane-1,1-bisphosphonic acids (220-222)

The tetraethyl cycloalkane-1,1-bisphosphonate (300 mg, 0.92 mmol) was treated with bromotrimethylsilane (1.2 cm^3, 9.2 mmol) in CH_2Cl (4 cm^3) under nitrogen for 48 h. The product was lyophilised, shaken with water (10 cm^3) and lyophillised again to yield the desired compound **(220-222)** as a colourless oil, which were converted into the bisdicyclohexylamine salts without any further purification.

6.3.19. Cyclobutane-1,1-bisphosphonic Acid (220)



(220)

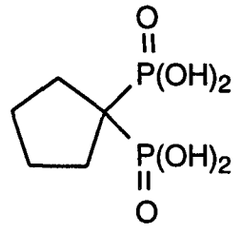
Cyclobutane-1,1-bisphosphonic acid **(220)** was prepared as described above (180 mg, 91%). δ_H (250 MHz; D_2O) 2.15 (4H, m, C(2)-H & C(4)-H), 2.45 (2H, m, C(3)-H); δ_C (63 MHz; D_2O) 21.53 (t, $^3J_{CP}$ 4.0, C-3), 26.92 (t, $^2J_{CP}$ 3.1, C-2 & C-4, 40.1 (t, J_{CP} 131, C-1); δ_P (162 MHz; D_2O) 26.2; (NH_3 CI) *m/z* 317 ($[M+H]^+$, 45), 299 (23), 281 (14) 253, 188 (100).

6.3.20. Bisdicyclohexylammonium Cyclobutane-1,1-bisphosphonic Acid (223)

Treatment of cyclobutane-1,1-bisphosphonic acid **(220)** (150 mg, 0.69 mmol) with ethanol (4 cm^3) and dicyclohexylamine (126 mg, 0.49 mmol) yielded the crude title compound which was recrystallised from

methanol/diethyl ether to give dicyclohexylammonium cyclobutane-1,1-bisphosphonic acid (223) as a white crystalline solid (251 mg, 91 %). m.p. 242-245 °C (Found C, 57.83; H, 9.70; N, 4.81; $C_{16}H_{33}NO_6P_2$ requires C, 58.09; H, 9.76; N, 4.84%).

6.3.21. Cyclopentane-1,1-bisphosphonic Acid (221)



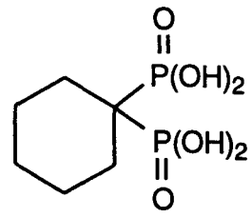
(221)

Cyclopentane-1,1-bisphosphonic acid **(221)** was prepared as described above (257 mg, 90%). δ_H (250 MHz; D_2O) 1.71 (4H, m, C(3)-H & C(4)-H), 2.08 (4H, m, 6.8, 4H, C(2)-H, C(5)-H); δ_C (63 MHz; D_2O) 29.9 (t, $^3J_{CP}$ 13.7, C-3 & C-4), 33.9 (t, $^2J_{CP}$ 2.8, C-2 & C-5), 47.1 (t, J_{CP} 126.9, C-1); δ_P (162 MHz; D_2O) 26.2; (NH_3 CI) *m/z* 231 ($[M+H]^+$, 60 %), 213, (14), 195 (15), 188 (100).

6.3.22. Bisdicyclohexylammonium Cyclopentane-1,1-bisphosphonic Acid (224)

Cyclopentane-1,1-bisphosphonic acid **(221)** (200 mg, 0.87 mmol) was treated with ethanol (5 cm^3) and dicyclohexylamine (160 mg, 0.87 mmol). The crude compound was recrystalised from methanol/diethyl ether to yield the title compound **(224)** as a white crystalline solid (320 mg, 90 %). m.p. 240-243 °C (Found C, 58.76; H, 9.92; N, 4.58; $C_{17}H_{35}NO_6P_2$ requires C, 58.71; H, 9.87; N, 4.73 %).

6.3.23. Cyclohexane-1,1-bisphosphonic Acid (222)



(222)

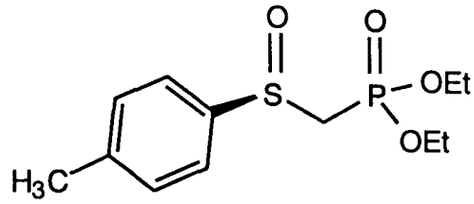
Cyclohexane-1,1-bisphosphonic acid **(222)** was prepared as described above (228 mg, 85 %). δ_H (250 MHz; D_2O) 1.38-1.53 (2H, m, C(4)-H), 1.65 (4H, quint, *J* 6.1, C(3)-H & C(5)-H), 1.86-2.13 (4H, m, C(2)-H & C(6)-H); δ_C (250 MHz; D_2O) 22.93 (t, $^3J_{CP}$ 6.1, C-3 & C-5), 27.82 (t, $^2J_{CP}$ 3.4, C2- & C-6), 27.75 (C-4), 41.55 (t, J_{CP} 116, C-1); δ_P (162 MHz; D_2O) 26.2; ((NH_3) CI) *m/z* 245 ($[M+H]^+$, 65).

6.3.24. Biscyclohexylammonium Cyclohexane-1,1-bisphosphonic Acid (225)

Cyclohexane-1,1-bisphosphonic acid **(222)** (200 mg, 0.82 mmol) was treated with ethanol (5 cm^3) and dicyclohexylamine (151 mg, 0.82 mmol). The crude compound was recrystallised from methanol/diethyl ether to yield the title compound **(225)** as a white crystalline solid (315 mg, 90 %). m.p. 214-216 °C (Found C, 59.21; H, 9.84; N, 4.55; $C_{30}H_{60}N_2O_6P_2$ requires C, 59.37; H, 9.97; N, 4.6%).

6.4 Synthesis of α-Phosphoryl Sulfoxides and Related Compounds

6.4.1. (-)-(*R*)-Diethyl Phosphorylmethyl *p*-Tolyl Sulfoxide (256)

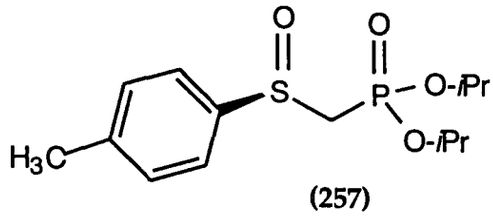


(256)

To a solution of diethyl methanephosphonate (2.5 g, 20 mmol) in anhydrous THF (50 cm^3) at -78 °C, under an atmosphere of nitrogen, was added a solution of *n*- butyl lithium (8.8 cm^3, 22 mmol). The mixture was stirred at -78 °C for 30 min. A solution of (-)-(1*R*,2*S*,5*R*)-menthyl-*p*-toluene sulfinate (4.3 g, 15 mmol) in anhydrous THF (10 cm^3) was added. After stirring at -78 °C for 30 min, the reaction mixture was warmed to -20 °C and quenched with saturated ammonium chloride solution. The organic solvent was removed under reduced pressure and the aqueous layer was washed with petroleum ether (2 x 20 cm^3) to remove the menthyl. The aqueous layer was then extracted with dichloromethane (3 x 30 cm^3). The combined organic layers were washed with brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. Excess diethyl methanephosphonate was removed by Kugelrohr distillation (50 °C, 0.1 mmHg) to leave the desired product which was further purified by silica gel chromatography (petroleum ether/ethyl acetate 1:3) to afford the title compound **(256)** (3.66 g, 84 %). $[\alpha]_D^{20}$ 147° (*c* 1.1 in acetone) (lit.,[192] 148° *c* 1 in acetone), (Found C, 49.56; H, 6.48; $C_{12}H_{19}O_4PS$ requires C, 49.62; H, 6.60 %); ϑ_{max}/cm^{-1} (neat) 2981, 1597, 1495, 1445, 1395, 1256, 1087, 1025; δ_H (250 MHz; $CDCl_3$) 1.20 (6H, m, OCH_2CH_3), 2.29 (3H, s, CH_3Ar), 3.17 & 3.29 (2H, J_{AB} 14.35, J_{AX} 15.50, AB of ABX system, CH_2P), 4.04 (4H, m, OCH_2CH_3), 7.38 (4H, A_2B_2 system, ArH); δ_C (63 MHz; $CDCl_3$) 16.13 (OCH_2CH_3), 21.32 (CH_3Ar), 53.66 (d,

J_{CP} 138, SCH_2P), 62.58 (OCH_2CH_3), 124.19, 129.8, (4C, Ar), 141.22 (1C, d, $^3J_{CP}$ 7, Ar), 142.19 (1C, Ar); δ_P (101 MHz; $CDCl_3$) 16.44; (EI) *m/z* 290 (M^+, 48 %), 262 (10), 234 (24), 139 (100), 105 (12), 91 (21), 65 (10).

6.4.2. (-)-(*R*)-Di-*iso*-propyl Phosphorylmethyl *p*-Tolyl Sulfoxide (257)

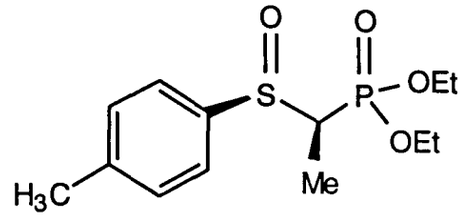


(257)

To a solution of di-*iso*-propyl methanephosphonate (2.5 g, 20 mmol) in anhydrous THF (50 cm^3) at -78 °C, under an atmosphere of nitrogen, was added a solution of *n*- butyllithium (8.8 cm^3, 22 mmol). The mixture was stirred at -78 °C for 30 min. A solution of (-)-(1*R*,2*S*,5*R*)-menthyl-*p*-toluenesulfinate (4.3 g, 15 mmol) in anhydrous THF (10 cm^3) was added. After stirring at -78 °C for 30 min, the reaction mixture was warmed to -20 °C and quenched with saturated ammonium chloride solution. The organic solvent was removed under reduced pressure and the aqueous layer was washed with petroleum ether (2 x 20 cm^3) to remove the menthyl. The aqueous layer was then extracted with dichloromethane (3 x 30 cm^3). The combined organic layers were washed with brine (2 x 20 cm^3), dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Excess di-*iso*-propyl methanephosphonate was removed by Kugelrohr distillation (55 °C, 0.1 mmHg) to leave the desired product which was purified by silica gel chromatography (petroleum ether/ethyl acetate 1:3) to afford the title compound **(256)** (2.85 g, 60 %). $[\alpha]_D^{20}$ 152° (*c* 1.2 in acetone), (Found C, 52.64; H, 7.14; $C_{14}H_{23}O_4PS$ requires C, 52.80; H, 7.29 %); ϑ_{max}/cm^{-1} (neat) 2983, 1583, 1478, 1445, 1395, 1255, 1085, 1025; δ_H (250 MHz; $CDCl_3$) 1.28 (12H, m, $OCH(CH_3)_2$), 2.26 (3H, s, CH_3Ar), 3.15 & 3.27 (2H, J_{AB} 14.60, J_{AX} 15.91, AB of ABX system, SCH_2P), 4.76 (2H, m, $OCH(CH_3)_2$), 7.30 (4H, A_2B_2 system, Ar);

δ_C (63 MHz; $CDCl_3$) 21.32 (CH_3Ar), 23.72 ($OCH(CH_3)_2$), 54.95 (d, J_{CP} 139, SCH_2P), 71.62 (d, $OCH(CH_3)_2$), 124.25, 129.83, (4C, Ar), 144.74 (1C, d, $^3J_{CP}$ 7.8, Ar), 142.01 (1C, Ar), ; δ_P (101 MHz; $CDCl_3$) 16.8; (EI) *m/z* 318 (M^+, 48 %), 276 (30), 220 (52), 139 (100), 105 (60), 91 (34), 77 (50), 65 (40).

6.4.3. (1*R*)-Diethyl 1-phosphorylethyl *p*-Tolyl (*R*)-Sulfoxide (265)

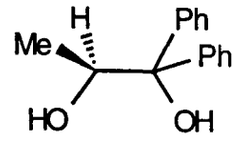


(265)

To a solution of diethyl phosphorylmethyl *p*-tolyl sulfoxide **(256)** (200 mg, 0.69 mmol) in dry THF (10 cm^3) at -78 °C under a nitrogen atmosphere, was added a *n*-butyllithium (0.29 cm^3, 0.73 mmol). The reaction mixture was stirred for 15 min and then a solution of iodomethane (200 mg, 1.39 mmol) in THF (1 cm^3) was added. The reaction mixture was warmed to room temperature and quenched with aqueous ammonium chloride solution (10 cm^3). The THF was removed under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 10 cm^3). The organic extracts were washed with water (2 x 10 cm^3) and brine (2 x 10 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to afford the crude product consisting of a mixture of the diastereoisomers in a ratio of 2.7:1 (as determined by ^{31}P nmr spectroscopy). Purification by silica gel chromatography (dichloromethane/methanol 4:1) yielded the major diastereoisomer **(265)** (140 mg, 66 %) $[\alpha]_D^{20}$ 154° (*c* 1.6 in acetone), δ_H (250 MHz; $CDCl_3$) 1.21 (6H, m, OCH_2CH_3), 1.30 (3H, dd, *J*=7.0 15.0, CH_3CHP), 2.21 (3H, s, CH_3Ar), 3.17 (1H, m, CH_3CHP), 4.04 (4H, m, OCH_2CH_3), 7.38 (4H, A_2B_2 system, ArH); δ_C (63 MHz; $CDCl_3$) 6.00 (d, $^2J_{CP}$=3.9, $SCH(CH_3)P$), 16.14 (d, $^3J_{CP}$=5.9, OCH_2CH_3), 21.31 (CH_3Ar), 44.07 (d, J_{CP}=138, $SCH(CH_3)P$), 62.73 (d, $^2J_{CP}$=6.9 OCH_2CH_3), 124.14 (129.85, 4C, Ar), 141.22 (1C, d, $^3J_{CP}$=7, Ar), 142.17

(1C, Ar),); δ_P (162 MHz; $CDCl_3$) 20.18; (EI) *m/z* 304 (M^+, 41 %), 276 (11), 248 (30), 139 (100), 105 (15), 91 (20), 65 (13).

6.4.4. (-)-(*S*)-1,1-Diphenyl 1,2-Dihydroxypropane (259)

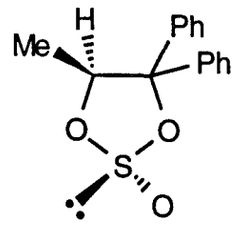


(259)

Magnesium turnings (75.36 g, 3 mol) and four crystals of iodine in anhydrous THF (400 cm^3) were placed in a dry 2 dm^3, 3-necked round bottom flask equipped with an overhead stirrer, condensor and pressure equalising dropping funnel, under a positive pressure of nitrogen. Bromobenzene (16 cm^3) was added to start the reaction, the remaining bromobenzene (300 cm^3) in anhydrous THF (400 cm^3)was added to the reaction mixture *via* the dropping funnel over a period of 90 min, allowing the reaction mixture to reflux gently. After the addition of the bromobenzene was complete the reaction mixture was heated to reflux for 3 h. After cooling to -5 °C, (*S*)-ethyl lactate was added keeping the temperature below 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by pouring the mixture in to a slush of ice and concentrated ammonium chloride solution (1 dm^3) and neutralising with 6 M hydrochloric acid solution. The mixture was then extracted with diethyl ether (4 x 250 cm^3), the combined etheral extracts were washed with water (4 x 200 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The crude product was recrystallised from cyclohexane to yield the title diol **(259)** (178 g, 78 %). m.p. 92-94 °C (lit.,[194] 94 °C) $[\alpha]_D^{20}$ -99.9° (*c* 1.8 in methanol) (lit.,[194] $[\alpha]_D^{20}$ -100°, c 1.8 in methanol), δ_H (250 MHz;

$CDCl_3$) 1.12 (3H, d, *J* 6.4, $CHCH_3$), 4.84 (1H, q, *J* 6.4, $CHCH_3$), 7.1-7.8 (10H, m, Ar); (EI) *m/z* 228 (M^+, 100 %), 210 (32), 182 (65), 91 (43), 77 (56), 65 (34).

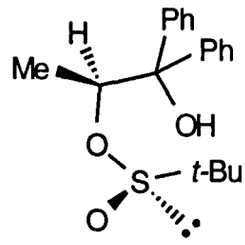
6.4.5. (-)-(2R,5S)-trans-4,4-Diphenyl-5-methyl-1,3,2-dioxathiolane 2-Oxide (260)



(260)

Triethylamine (30.5 cm^3, 0.22 mol) in dichloromethane (300 cm^3) was added dropwise to a solution of the (*S*)-diol **(259)** (25 g, 0.11 mol) and thionyl chloride (12 cm^3, 0.16 mol) in dichloromethane (200 cm^3) at -40 °C. Once the addition was complete a white precipitate appeared and the flask was warmed to 0 °C. The reaction was quenched by the addition of water (300 cm^3). The product was recovered by extraction with dichloromethane (2 x 100 cm^3). The combined organic extracts were washed with water (2 x 100 cm^3), concentrated sodium bicarbonate solution (4 x 75 cm^3) and brine (2 x 100 cm^3), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. The crude product was recrystallised from cyclohexane/hexane (1:1) to afford the desired compound (17 g, 56 %). m.p. 110-111 °C (lit.,[193] 109-111 °C) $[\alpha]_D^{20}$ -245.1° (*c* 1.1 in $CHCl_3$) (lit.,[193] $[\alpha]_D^{20}$ -246° *c* 1.1 in $CHCl_3$), (Found C, 65.75; H, 5.09; $C_{15}H_{14}O_3S$ requires C, 65.65; H, 5.15 %); δ_H (250 MHz; $CDCl_3$) 1.30 (3H, d, *J* 6.4, $CHCH_3$), 5.71 (1H, q, *J* 6.4, $CHCH_3$), 7.00 (, 2Hm, Ar), 7.31-7.52 (8H, m, Ar); δ_C (63 MHz; $CDCl_3$) 16.51 (CH_3), 80.37 ($CHCH_3$), 95.83 ($C(Ph)_2$), 126.7, 127.4, 128.01, 128.3, 128.6, 138.2, 140.3 (12C, Ar); (NH_3 CI) *m/z* 292 ($[M+NH_4]^+$, 60 %), 274 (M^+, 5), 228 (82), 211 (100), 195 (45), 183 (73), 165 (48), 105 (87)

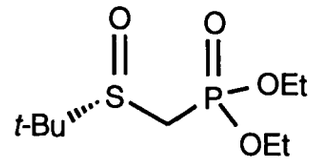
6.4.6. (-)-(1R,S*S*)-2,2-Diphenyl-1,2-dihydroxy-propyl 2-O-*t*-Butylsulfinate (262)



(262)

A solution of *t*-butyl magnesium chloride (36.5 cm^3, 1 M in THF) was added dropwise to a solution of the dioxathiolane **(260)** (10 g, 36.5 mmol) in anhydrous THF (100 cm^3) at -78 °C under an atmosphere of nitrogen. The reaction was followed by tlc (cyclohexane/ethyl acetate 5:1). When conversion was complete, the solution was quenched with saturated ammonium chloride solution, extracted with dichloromethane (2 x 50 cm^3), washed with water (2 x 40 cm^3) and brine (2 x 40 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude product was recrystallised from cyclohexane to afford the title compound **(262)** (8.5 g, 70 %). m.p. 137-138 °C (lit.,[193] 135-137 °C), $[\alpha]_D^{20}$ -121.8° (*c* 0.7 in $CHCl_3$) (lit.,[193] $[\alpha]_D^{20}$ -120° *c* 1.1 in $CHCl_3$), (Found C, 68.72; H, 7.31; $C_{19}H_{24}O_3S$ requires C, 68.64; H, 7.21 %); δ_H (250 MHz; $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 1.39 (3H, d, *J* 6.4, $CHCH_3$), 3.00 (1H, s, OH), 5.36 (1H, q, *J* 6.4, $CHCH_3$), 7.15-7.65 (10H, m, ArH); δ_C (63 MHz; $CDCl_3$) 16.24 ($CHCH_3$), 21.47 ($CH(CH_3)_3$), 57.71 ($CH(CH_3)_3$), 79.63 ($CHCH_3$), 82.43 ($C(Ph)_2$), 125.51, 126.02, 126.93, 127.00, 128.1, 128.2, 143.1, 145.1 (12C, Ar); (NH_3 CI) *m/z* 250 ($[M+NH_4]^+$, 48 %), 233 ($[M+H]^+$, 32 %), 276 (24), 228 (44), 165 (48), 105 (87).

6.4.7. (+)-(*S*)-Diethyl Phoshorylmethyl *t*-Butyl Sulfoxide (263)

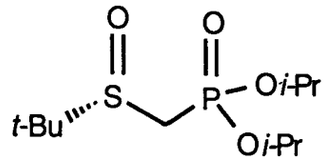


(263)

n-Butyllithium (1.23 cm^3, 3.08 mmol) was added to a solution of the sulfinate **(262)** (1.02 g, 3.08 mmol) in anhydrous THF (50 cm^3) at -78 °C under an atmosphere of nitrogen. To this solution, *via* a transfer needle, was added a solution of α-lithio diethyl methanephosphonate which had been prepared by the addition of n-butyllithium (3.1 cm^3, 7.7 mmol) to diethyl methanephosphonate (1.17 g, 7.7 mmol) in anhydrous THF (20 cm^3) at -78 °C. The reaction mixture was stirred at -78 °C for 2 h, warmed to room temperature and quenched with saturated ammonium chloride solution (20 cm^3). The THF was removed under reduced pressure and the aqueous solution extracted with petroleum ether (2 x 15 cm^3) to remove the diol. The crude product was isolated by extraction of the aqueous layer with dichloromethane (4 x 20 cm^3). The dichloromethane extracts were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Excess diethyl methanephosphonate was removed by Kugelrohr distillation. Purification using silica gel chromatography (ethyl acetate) afforded the title compound (482 mg, 61 %). $[\alpha]_D^{20}$ -73° (*c* 1.2 in acetone), (Found C, 42.25; H, 8.41; $C_9H_{21}O_4PS$ requires C, 42.16; H, 8.26 %); ϑ_{max}/cm^{-1} (neat) 2984, 2973, 2887, 2858, 1495, 1445, 1392, 1255, 1027; δ_H (250 MHz; $CDCl_3$) 0.98 (9H, s, $CH(CH_3)_3$), 1.04 (6H, t, *J* 7.8, OCH_2CH_3), 2.36 & 2.73 (2H, J_{AB} 14.81, J_{AX} 18.00, AB of ABX system, SCH_2P), 3.89 (4H, m, OCH_2CH_3); δ_C (63 MHz; $CDCl_3$) 16.41 (d, $^3J_{CP}$=4.8, OCH_2CH_3), 23.54 ($C(CH_3)_3$), 43.22 (d, J_{CP} 144, SCH_2P), 54.36 (d, $^3J_{CP}$ 7, $C(CH_3)_3$), 62.4 (d, $^2J_{CP}$=5.9, OCH_2CH_3); δ_P (101 MHz; $CDCl_3$) 18.2;

(NH_3 CI) *m/z* 257 ([M+H]$^+$, 75 %), 229 (40), 201 (42), 183 (31), 144 (10), 108 (13), 58 (60), 41 (100).

6.4.8. (+)-(*S*)-Di-*iso*-propyl Phoshorylmethyl *t*-Butyl Sulfoxide (264)



(264)

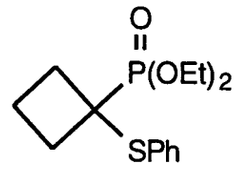
n-Butyllithium (2.5 cm^3, 5 mmol) was added to a solution of the sulfinate **(262)** (1.66 g, 5 mmol) in anhydrous THF (70 cm^3) at -78 °C under an atmosphere of nitrogen. To this solution, *via* a transfer needle, was added a solution of α-lithio di-*iso*-propyl methanephosphonate which had been prepared by the addition of *n*-butyllithium (5.0 cm^3, 10 mmol) to di-*iso*-propyl methanephosphonate (1.8 g, 10 mmol) in anhydrous THF (20 cm^3) at -78 °C. The reaction mixture was stirred stirred at -78 °C for 2 h, warmed to room temperature and quenched with saturated ammonium chloride solution (20 cm^3). The THF was removed under reduced pressure and the aqueous solution extracted with petroleum ether (2 x 20 cm^3) to remove the diol. The crude product was isolated by extraction of the aqueous layer with dichloromethane (4 x 25 cm^3). The dichloromethane extracts were washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate and the solvent removed in vacuo. Excess di-*iso*-propyl methanephosphonate was removed by Kugelrohr distillation. Purification using silica gel chromatography (ethyl acetate) afforded the title compound **(264)** as a colourless oil (924 mg, 66 %). $[\alpha]_D^{20}$ 81.8° (*c* 1 in acetone), (Found C, 46.52; H, 8.99; $C_{11}H_{25}O_4PS$ requires C, 46.44; H, 8.87 %); ϑ_{max}/cm^{-1} (neat) 2982, 2972, 2889, 2855, 1495, 1443, 1392, 1256, 1028; δ_H (250 MHz; $CDCl_3$) 0.98 (9H, s, C(CH_3)$_3$), 1.08 & 1.10 (12H, d, *J* 6.1 & 6.1, CH(CH_3)$_2$), 2.39 & 2.71 (2H,

J_{AB} 14.83, J_{AX} 18.00, AB of ABX system, SCH_2P), 3.89 (2H, m, OCH(CH_3)); δ_C (63 MHz; $CDCl_3$) 23.67 (C(CH_3)$_3$), 24.71 (OCH(CH_3)$_2$), 43.44 (d, J_{CP} 144, SCH_2P), 54.42 (d, $^3J_{CP}$ 7, C(CH_3)$_3$), 71.44 (OCH(CH_3)$_2$); δ_P (101 MHz; $CDCl_3$) 18.34; (NH_3 CI) *m/z* 285 ([M+H]$^+$, 80 %), 269 (40), 229 (33), 181 (15), 163 (19), 108 (11), 58 (66), 41 (100).

6.4.9. General Procedure for the Synthesis of Diethyl 1-Phosphorylcycloalkane Phenyl Sulfides

A solution of freshly prepared LDA (3.84 mmol) in anhydrous THF (10 cm^3) was added to a solution of diethyl phosphorylmethyl phenyl sulfide (1 g, 3.84 mmol) in anhydrous THF (20 cm^3) at -78 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 1 h and then the appropriate 1,ω-dibromoalkane (3.84 mmol) in anhydrous THF (2 cm^3) was added. The reaction mixture was allowed to warm to room temperature over a period of 1 h, at which time the reaction mixture was re-cooled to -78 °C and a second equivalent of LDA (3.84 mmol) in anhydrous THF (10 cm^3) was added. The reaction mixture was stirred at -78 °C for 1 h, then warmed to room temperature and quenched with a saturated solution of ammonium chloride (20 cm^3). The THF was removed under reduced pressure and the aqueous solution extracted with dichloromethane (3 x 20 cm^3), the organic extracts were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by Kugelrohr distillation (160-170 °C, 0.1 mmHg) to afford the desired compounds.

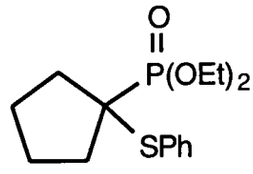
6.4.10. Diethyl 1-Phosphorylcyclobutane Phenyl Sulfide (121)



(121)

Diethyl 1-phosphorylcyclobutane phenyl sulfide **(121)** was prepared as described above (710 mg, 62 %). δ_H (250 MHz; $CDCl_3$) 1.15 (6H, t, *J* 7, OCH_2CH_3), 1.91-2.15 (4H, br. m, C(2)-H & C(4)-H), 2.48-2.65 (2H, br. m, C(3)-H), 3.90 (4H, m, OCH_2CH_3), 7.13 (3H, m, ArH), 7.51 (m, 2H, ArH); δ_C (63 MHz; $CDCl_3$) 16.15 (d, $^3J_{CP}$ 5.8, OCH_2CH_3), 16.59 (d, $^3J_{CP}$ 10.2, C-3), 30.10 (d, $^2J_{CP}$ 1.5, C(2) & C-4), 44.85 (d, J_{CP} 151.4, C-1), 62.23, (d, J=5.4, OCH_2CH_3),127.92, 128.22, 128.67, 134.62 (6C, Ar); δ_P (162 MHz; $CDCl_3$) 19.5; (EI) *m/z* 300 (M^+, 32 %), 272 (24), 228 (35), 109 (100), 77 (67).

6.4.11. Diethyl 1-Phosphorylcyclopentane Phenyl Sulfide (266)

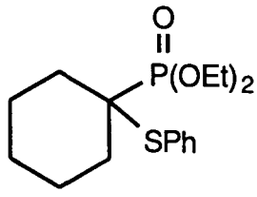


(266)

Diethyl 1-phosphorylcyclopentane phenyl sulfide **(266)** was prepared as described above (688 mg, 57 %). δ_H (250 MHz; $CDCl_3$) 1.15 (6H, t, *J* 7, OCH_2CH_3), 1.64-2.13 (8H, br. m, C(2)-H, C(3)-H, C(4)-H & C(5)-H), 4.04 (4H, m, OCH_2CH_3), 7.18 (3H, m, ArH), 7.62 (2H, m, ArH); δ_C (63 MHz; $CDCl_3$) 16.13 (d, $^3J_{CP}$ 5.8, OCH_2CH_3), 23.12 (d, $^3J_{CP}$ 9.9, C-3 & C-4), 35.61 (d, $^2J_{CP}$ 1.8, C-2 & C-5), 49.45 (d, J_{CP} 151.4, C-1), 62.32 (d, $^2J_{CP}$=5.9, OCH_2CH_3), 127.94,

128.32, 128.64, 134.61 (6C, Ar); δ_P (162 MHz; $CDCl_3$) 19.34; (EI) *m/z* 314 (M^+, 39), 286 (35), 242 (31), 109 (100), 77 (59).

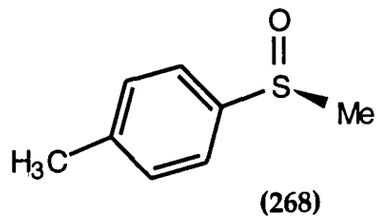
6.4.12. Diethyl 1-Phosphorylcyclohexane Phenyl Sulfide (267)



(267)

Diethyl 1-phosphorylcyclohexane phenyl sulfide **(267)** was prepared as described above (667 mg, 53 %). δ_H (250 MHz; $CDCl_3$) 1.09 (6H, t, *J* 7, OCH_2CH_3), 1.0-1.85 (10H, br. m, C(2)-H, C(3)-H, C(4)-H, C(5)-H & C(6)-H_2), 3.94 (4H, m, OCH_2CH_3), 7.12 (3H, m, Ar), 7.71 (2H, m, Ar); δ_C (63 MHz; $CDCl_3$) 16.17 (d, $^3J_{CP}$ 5.8, OCH_2CH_3), 21.09 (d, $^3J_{CP}$ 10.7, C-3 & C-5), 32.32 (d, $^2J_{CP}$ 4.3, C-2 & C-6), 58.81 (d, J_{CP} 148.4, C-1), 62.28 (d, $^2J_{CP}$=5.9, OCH_2CH_3), 127.91, 128.35, 128.63, 134.65 (6C, Ar); δ_P (101 MHz; $CDCl_3$) 19.28; (EI) *m/z* 328 (M^+, 41 %), 298 (31), 256 (33), 109 (100), 77 (43).

6.4.13. (+)-(*S*)-Methyl Tolyl Sulfoxide (268)

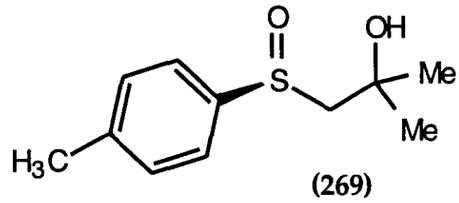


(268)

To a solution of (-)-(1R,2*S*,5*R*)-menthyl-*p*-toluenesulfinate (4 g, 13.4 mmol) in anhydrous THF (60 cm^3) at -78 °C under an atmosphere of nitrogen, was added a solution of methylmagnesium bromide (6.71 cm^3, 3M in Et_2O). The reaction mixture was stirred for 1 h, warmed to 0 °C and quenched with

saturated solution of ammonium chloride solution (15 cm^3). The product was isolated by extraction into ether (2 x 30 cm^3). The combined organic layers were washed with water (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude product was purified by silica gel chromatography (ethyl acetate) affording the title compound **(268)** (1.6 g, 77 %). $[\alpha]_D^{20}$ +181° (*c* 1.2 in $CHCl_3$), δ_H (250 MHz; $CDCl_3$) 2.40 (3H, s, ArCH_3), 2.69 (3H, s, S(O)CH_3), 7.30 (2H, d, *J* 8.4, Ar), 7.51 (2H, d, *J* 8.4, Ar); (EI) *m/z* 154 (M^+, 58 %), 139 (100), 91 (60), 77 (20), 65 (28).

6.4.14. (+)-(*R*)-2,2-dimethyl-2-hydroxymethyl *p*-Tolyl Sulfoxide (269)

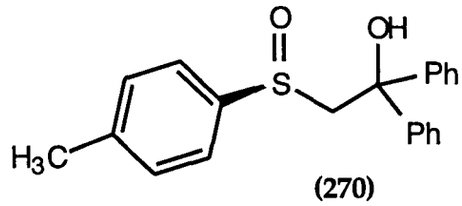


(269)

To a solution of (-)-(*S*)-methyl tolyl sulfoxide **(268)** (750 mg, 4.9 mmol) in anhydrous THF (20 cm^3) at -78 °C under an atmosphere of nitrogen, was added *n*-butyllithium (2.1 cm^3, 5.3 mmol). The reaction mixture was stirred for 30 min and anhydrous acetone (2 cm^3) was added. The reaction mixture was warmed to 0 °C and quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed *in vacuo* and the aqueous solution extracted with dichloromethane (3 x 20 cm^3). The combined organic layers were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. Recrystallisation of the crude compound from diethyl ether containing a few drops of ethanol yielded the desired compound **(269)** (852 mg, 82 %). m.p. 92-94° $[\alpha]_D^{20}$ +201° (*c* 2 in acetone), (Found C, 62.40; H, 7.60; $C_{11}H_{16}O_2S$ requires C, 62.21; H, 7.60 %); δ_H (250 MHz; $CDCl_3$) 1.33 (3H, s,

C(OH)CH_3), 1.54 (3H, s, C(OH)CH_3), 2.67 & 2.96 (2H, d, J_{AB} 13.4, AB system, S(O)CH_2), 7.27 (2H, d, J 7.85, Ar), 7.48 (2H, d, J 7.85, Ar); δ_C (63 MHz; $CDCl_3$) 21.31 (ArCH_3), 28.90 (C(OH)CH_3), 30.34 (C(OH)CH_3), 68.44 (S(O)CH_2), 70.54 (C(OH)$(CH_3)_2$), 123.84, 130.02, 140.55, 141.71 (6C, Ar); (EI) m/z 212 (M^+, 8 %), 196 (16), 140 (100), 123 (22), 91 (74), 77 (19).

6.4.15. (+)-(*R*)-2,2-Diphenyl-2-hydroxymethyl *p*-Tolyl Sulfoxide (270)



(270)

To a solution of (-)-(*S*)-methyl tolyl sulfoxide **(268)** (750 mg, 4.9 mmol) in anhydrous THF (20 cm^3) at -78 °C under an atmosphere of nitrogen, was added *n*-butyllithium (2.1 cm^3, 5.3 mmol). The reaction mixture was stirred for 30 min and benzophenone (885 mg, 4.86 mmol) was added. The reaction mixture was warmed to 0 °C and quenched with a saturated solution of ammonium chloride (10 cm^3). The THF was removed *in vacuo* and the aqueous solution extracted with dichloromethane (3 x 20 cm^3). The combined organic layers were washed with water (2 x 15 cm^3) and brine (2 x 15 cm^3), dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude compound was purified using silica gel chromatography (petroleum ether/ethyl acetate 7:3) and recrystallised from diethyl ether to yield the desired compound **(270)** (1.23 g, 73 %). m.p. 141-143 °C $[\alpha]_D^{20}$ 184.3° (*c* 2 in acetone), (Found C, 74.75; H, 6.04; $C_{21}H_{20}O_2S$ requires C, 74.95; H, 5.99 %); δ_H (250 MHz; $CDCl_3$) 2.42 (3H, ArCH_3), 3.55 & 3.64 (2H, J_{AB} 13.74, AB system, S(O)CH_2), 5.91 (1H, OH), 7.23-7.71 (14H, br. m, ArH); δ_C (63 MHz; $CDCl_3$) 21.41 (ArCH_3), 66.41 (S(O)CH_2), 78.29 (C(OH)$(Ph)_2$), 123.99, 125.53, 126.57, 127.38, 127.55, 128.24, 128.48, 130.15, 140.31, 142.20, 144.08, 145.90 (18C,

Ar); (EI) *m/z* 336 (M^+, 10 %), 258 (24), 140 (100), 123 (28), 105 (15), 91 (80), 77 (22), 65 (30).

6.4.16. General Procedure for Diethylzinc Reactions

A solution of the appropriate catalyst (10 mol %) in hexane (2 cm^3) was added to a solution of benzaldehyde (1 g, 9.4 mmol) in hexane (8 cm^3) and the solution was cooled to -5 °C. Diethylzinc (18.9 mmol, 1 M solution in hexane) was added slowly to the reaction mixture. After completing this addition, the reaction mixture was allowed to slowly warm to room temperature. Samples of the reaction mixture were analysed by ^1H nmr spectroscopy until the signal due to the aldehydic proton was absent, indicating quantitative reaction, at which time ethanol (5 cm^3) was added to the reaction mixture and the organic solvent was removed under reduced pressure. The residue was dissolved in dilute hydrochloric acid (1 M, 20 cm^3) and extracted with diethyl ether (3 x 40 cm^3). The ethereal extracts were washed with dilute hydrochloric acid (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by Kugelrohr distillation (100 °C, 0.1 mmHg) to afford pure 1-phenyl-1-propanol. The optical rotation of the alcohol was determined. δ_H (250 MHz; $CDCl_3$) 1.05 (3H, t, *J* 6.7, CH_2CH_3), 1.85 (2H, m, $CHCH_2CH_3$), 3.52 (br. s, OH), 4.66 (1H, t, *J* 4.8, $CH(OH)(CH_2)$), 7.52 (5H, s, ArH).

6.4.17. General Procedure for Diethylzinc Reaction with Titanium Tetra-*iso*-propoxide

A solution of the appropriate catalyst (10 mol %) and titanium tetra-*iso*-propoxide (3.96 g, 9 mmol) in hexane (5 cm^3) was heated to reflux for 20 min, cooled to -5 °C and added to a solution of benzaldehyde (1 g, 9.4 mmol) in hexane (8 cm^3) at -5 °C. Diethylzinc (18.9 mmol, 1 M solution in hexane)

was added slowly to the reaction mixture, after completing this addition the reaction mixture was slowly allowed to warm to room temperature. Samples of the reaction mixture were analysed by ^{1}H nmr spectroscopy until the signal due to the aldehydic proton was absent, indicating quantitative reaction. At which time ethanol (5 cm^3) was added to the reaction mixture and the organic solvent removed under reduced pressure. The residue was dissolved in dilute hydrochloric acid (1 M, 20 cm^3) and extracted with diethyl ether (3 x 40 cm^3). The ethereal extracts were washed with dilute hydrochloric acid (2 x 20 cm^3) and brine (2 x 20 cm^3), dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by Kugelrohr distillation (100 °C, 0.1 mmHg) to afford pure 1-phenyl-1-propanol. The optical rotation of the alcohol was determined.

References

1. J. Pikl, US patent 2.328.358, 1943 (CA **38:**4587, 1943).

2. R.L. Hilderbrand and T.O. Henderson, *Phosphonic acids in nature*, CRC Press, Florida, 1983.

3. F. Hammerschmidt, *Liebigs. Ann. Chem.*, 1988, 531.

4. F. Hammerschmidt, *Liebigs Ann. Chem.*, 1988, 537.

5. F. Hammerschmidt, *Liebigs Ann. Chem.*, 1988, 955.

6. J. Krapcho, C. Turk, D.W. Cushman, J.R. Powell, J.M. DeForrest, E.R. Spitzmiller, D.S. Karanewsky, M. Duggan, G. Rovnvak, J. Schwartz, S. Natarajan, J.D. Godfrey, D.E. Ryono, R. Neubeck, A.K. S. and E.W. Petrillo Jr., *J. Med. Chem.*, 1988, **31**, 1148.

7. D.S. Karanewsky, M.C. Badia, D.W. Cushman, J.M. DeForrest, T. Dejneka, M.J. Loots, M.G. Perri, E.W. Petrillo Jr. and J.R. Powell, *J. Med. Chem.*, 199488, **31**, 204.

8. M.D. Erion and C.T. Walsh, *Biochem. J.*, 1987, **26**, 3417.

9. U. Groth, L. Lehmann, L. Richter and U. Schöllkopf, *Liebigs Ann. Chem.*, 1993, 427.

10. K. Hiroshi, Y. Masayuki, K. Toshiro, O. Ryo, M. K. and S. Kunikatsu, European Patent, EP 61,172, 1982, (CA **98:**1077933, 1983)

11. B. Lejczak, P. Kafarski and E. Makowiecka, *Biochem. J.*, 1987, **242**, 81.

12. P. Kafarski and B. Lejczak, *Phosphorus, Sulfur and Silicon*, 1991, **63**, 193.

13. E. Bayer, K.H. Gugel, K. Hägele, H. Hagenmaier, S. Jessipow, W.A. König and H. Zähner, *Helv. Chim. Acta*, 1972, **55**, 224.

14. S. Omura, K. Hinotazawa, N. Imamura and M. Murata, *J. Antibiot.*, 1984, **32**, 939.

15. I. Natchev, *J. Chem. Soc., Perkin Trans.1*, 1989, 125.

16. B.K. Park, A. Hirota and H. Sakai, *Agr. Biol. Chem.*, 1976, **40**, 1905.

17. C. Rapp, M. Jung, M. Kugler and W. Loeffler, *Liebigs Ann. Chem.*, 1988, 655.

18. M. Okuhara and T. Goto, *Drugs Expl. Res.*, 1981, **7**, 559.

19. B. Lauber, S.D. Lindell and H.D. Pohlenz, *Arch. Microbiol.*, 1994, **161**, 400.

20. F.R. Atherton, C.H. Hassall and R.W. Lambert, *J. Med. Che,*, 1986, **29**, 29.

21. G. Hoerlein, *Rev. Environ. Contam. Toxicol.*, 1994, **138**, 73.

22. H.-J. Zeiss, *Tetrahedron*, 1992, **48**, 8263.

23. M.G. Hoffmann and H.-J. Zeiss, *Tetraheron Lett.*, 1992, **33**, 2669.

24. H.-J. Zeiss, *Tetrahedron Lett.*, 1987, **28**, 1255.

25. H.-J. Zeiss, *J. Org. Chem.*, 1991, **56**, 1783.

26. I.V. Natchev, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3699.

27. I.V. Natchev, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 3705.

28. E.W. Logusch, D.M. Walker, J.F.L. McDonald, Leo G. C. and J.E. Franz, *J. Org. Chem.*, 1988, **53**, 4069.

29. H. Seto, S. Sasaki, S. Imay, T. Tsuroka, H. Ogawa, A. Satoh, S. Inouye, T. Niida and N. Otake, *J. Antibiot.*, 1983, **36**, 96.

30. E.K. Baylis, C.D. Campbell and J.G. Dingwall, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2845.

31. H.C. Steirüken and N. Amrhein, *Biochem. Biophys. Res. Commun.*, 1980, **94**, 1207.

32. I.A. Natchev, *Tetrahedron*, 1988, **44**, 1511.

33. J.C. Watkins, P. Krogsgaard-Larsen and T. Honoré, *Trends. Pharmacol. Sci.*, 1990, **11**, 25.

34. G.L. Collingridge and W. Singer, Elsevier, Cambridge, 1991, 42.

35. B. Meldrum and J. Garthwaite, *Excitatory amino acid neurotoxicity and neurodegenerative disease.*, Elsevier, Cambridge, 1991.

36. J.S. Teitelbaum, R.J. Zatore, S. Carpenter, D. Gendron, A.C. Evans, A. Gjedde and N.R. Cashman, *New Engl. J. Med.*, 1990, **322**, 1781.

37. T. Hayashi, *Keio J. Med.*, 1954, **3**, 1831.

38. J.C. Watkins and R.H. Evans, *Ann. Rev. Pharmacol. Toxicol.*, 1981, **21**, 165.

39. J.J. Hansen and P. Krogsgaard-Larsen, *Med. Res. Rev.*, 1990, **10**, 55.

40. P.M. Headley and S. Grillner, in *Excitatory Amino Acids and synaptic transmission: the evidence for physiological function.*, ed. P.M. Headley and S. Grillner, Elsevier, Cambridge, 1991.

41. F. Sladeczek, M. Recasens and J. Bockaert, *Trends Neurosci.*, 1988, **11**, 546

42. J. Watkins and G. Collingridge, *Trends Pharmacol. Sci.*, 1994, **15**, 333.

43. W.H. Lunn, D.D. Schoepp, D.O. Calligaro, R.T. Vasilef, L.J. Heinz, C.R. Salhoff and J.O. O'Malley, *J. Med. Chem.*, 1992, **35**, 4608.

44. R.D. Allan, J.R. Hanrahan, T.W. Hambley, G.A.R. Johnston, K.N. Mewett and A.D. Mitrovic, *J. Med. Chem.*, 1990, **33**, 2905.

45. E.A. Bell, M.Y. Quereshi, R.J. Pryce, D.H. Janzen, P. Lemke and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 1409.

46. C.F. Bigge, J.T. Drumond, G. Johnson, T. Malone, A.W. Probert Jr., F.W. Marcoux, L.L. Coughenour and L.J. Brache, *J. Med. Chem.*, 1989, **32**, 1580.

47. R.L. Johnson and J.F. Koerner, *J. Med. Chem.*, 1988, **31**, 2056.

48. H. McLennan, *Prog. Neurobiol.*, 1983, **20**, 251.

49. J. Davies, A.A. Francis, A.W. Jones and J.C. Watkins, *Neurosci. Letts.*, 1980, **21**, 77.

50. M.N. Perkins, T.W. Stone, J.F. Collins and K. Curry, *Neurosci. Letts.*, 1981, **23**, 333.

51. W.A. Kinney, N.E. Lee, D.T. Garrison, E.J. Podlesney Jr, J.T. Simmonds, D. Bramlett, R.R. Notvest, D.M. Kowal and R.P. Tasse, *J. Med. Chem.*, 1992, **35**, 4720.

52. J.P. Whitten, B.M. Baron, D. Muench, F. Miller, H.S. White and I.A. McDonald, *J. Med. Chem.*, 1990, **33**, 2961.

53. J. Lehmann, J. Schneider, S. McPherson, D.E. Murphy, P. Bernard, C. Tsai, D.A. Bennett, G. Pastor, D.J. Steel, C. Boehm, D.L. Cheney, J.M. Liebman, M. Williams and P.L. Wood, *J. Pharmacol. Exp. Ther.*, 1986, **240**, 737.

54. J. Lehmann, A.G. Chapman, B.S. Meldrum, A. Hutchinson, C. Tsai and P.L. Wood, *European J. Pharmacol.*, 1988, **154**, 89.

55. A.J. Hutchinson, M. Williams, C. Angst, R. de Jesus, L. Blanchard, R.H. Jackson, E.J. Wilusz, D.E. Murphy, P.S. Bernard, J. Schneider, T. Campbell, W. Guide and M.A. Sills, *J. Med. Chem.*, 1989, **32**, 2171.

56. C.F. Bigge, G. Johnson, D.F. Ortwine, J.T. Drummond, D.M. Retz, L.J. Brahce, L.L. Coughenour, F.W. Marcoux and A.W. Probert, *J. Med. Chem.*, 1992, **35**, 1371.

57. A. Dorville, I. McCort-Tranchepain, D. Vichard, W. Sather, R. Maroun, P. Ascher and B.P. Roques, *J. Med. Chem.*, 1992, **35**, 2551.

58. D.F. Ortwine, T.C. Malone, C.F. Bigge, J.T. Drummond, C. Humblet, G. Johnson and G.W. Pinter, *J. Med. Chem,*, 1992, **35**, 1345.

59. J.P. Whitten, B.L. Harrison, J.R.W. Weintraub and I.A. McDonald, *J. Med. Chem.*, 1992, **35**, 1509.

60. P. Krogsgaard-Larsen, T. Honoré, J.J. Hansen, D.R. Curtis and D. Lodge, *Nature*, 1980, **284**, 64.

61. N. Skjæræk, B. Ebert, E. Falch, L. Brehm and P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1*, 1995, 221.

62. T. Honoré, S.D. Davies, J. Drejer, E.J. Fletcher, P. Jacobsen, D. Lodge and F.E. Nielsen, *Science*, 1988, **241**, 701.

63. J.A. Monn and D.D. Schoepp, *Ann. Rep. Med. Chem.*, 1994, **29**, 53.

64. S. Haldeman and H. McLennan, *Brain Res.*, 1972, **45**, 393.

65. P. Krogsgaard-Larsen, J.W. Ferkany, E.Ø. Nielsen, B. Ebert, J.S. Johansen, N.H. Diemer, T. Bruhn, D.T. Beattie and D.R. Curtis, *J. Med Chem.*, 1991, **34**, 123.

66. A.B. Young and G.E. Fagg, in *Excitatory Amino Acids in the brain: membrane binding and receptor autoradiographic approaches.*, ed. A.B. Young and G.E. Fagg, Elsevier, Cambridge, 1991.

67. M.K. Schulte, R.J. Roon, D.J. Chalmers, D.C. Sunter and J.F. Koerner, *Brain Res.*, 1994, **649**, 203.

68. M.K. Schulte, E.R. Whittemore, J.F. Koerner and R.L. Johnson, *Brain. Res.*, 1992, **582**, 291.

69. N.L. Peterson, H.B. Kroona, R.L. Johnson and J.F. Koerner, *Brain Res.*, 1992, **571**, 162.

70. E. Palmer, D.T. Monaghan and C.W. Cotman, *Eur. J. Pharmacol.*, 1989, **166**, 585.

71. Y. Nakagawa, K. Saitoh, T. Ishihara, M. Ishida and H. Shinozaki, *Eur. J. Pharmacol.*, 1990, **184**, 205.

72. D. Schoepp, J. Bockaert and F. Sladeczek, *Excitatory amino acid neurotoxicity and neurodegenerative disease.*, Elsevier, Cambridge, 1991.

73. J.A. Saugstad, T.P. Segerson and G.L. Westbrook, *Eur. J. Pharmacol.*, 1995, **289**, 395.

74. L. Littman, B.S. Glatt and M.B. Robinson, *J. Neurochem.*, 1993, **61**, 586.

75. P.E. Pigou and C.H. Schiesser, *J. Org. Chem.*, 1988, **53**, 3841.

76. A.J. Sutherland, unpublished work.

77. S.L. Crooks, M.B. Robinson, J.F. Koerner and R.L. Johnson, *J. Med. Chem.*, 1986, **29**, 1988.

78. O. Kikuchi, *Bull. Chem. soc. Jpn.*, 1982, **55**, 1669.

79. M.S. Dappen, R. Pellicciari, B. Natalini, J.B. Monaham, C. Chiorri and A.A. Cordi, *J. Med. Chem.*, 1991, **34**, 161.

80. M. Avram, C.D. Nenitzescu and M. Maxim, *Chem. Ber.*, 1957, **90**, 1424.

81. R.R. Gallucci and R. Going, *J. Org. Chem.*, 1981, **46**, 2532.

82. M.E. Jung and M.A. Lyster, *J. Org. Chem.*, 1977, **42**, 3761.

83. C.J. Michejda and R.W. Comnick, *J. Org. Chem.*, 1975, **40**, 1046.

84. K.B. Wieberg, G.M. Lampman, R.P. Ciula, D.S. Conner, P. Schertler and J. Lavanish, *Tetrahedron*, 1965, **21**, 2749.

85. A.K. Bhattacharya and G. Thyagarajan, *Chem. Rev.*, 1981, **81**, 415.

86. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1945, **67**, 1180.

87. J.J. Eisch, S.K. Dua and M. Behrooz, *J. Org. Chem.*, 1985, **50**, 3674.

88. J.M. Decesare, B. Corbel, T. Durst and J.F. Blount, *Can. J. Chem.*, 1981, **59**, 1415.

89. M. Mikolajczyk, W. Midura, S. Grzejszczak, A. Zatorski and A. Chefczynska, *J. Org. Chem.*, 1978, **43**, 473.

90. M. Mikolajczyk, S. Grzejszczak and A. Zatorski, *J. Org. Chem.*, 1975, **40**, 1979.

91. M. Mikolajczyk and W. Midura, *Phosphorus Sulfur*, 1988, **36**, 1988.

92. P.L. Coe, S. Jones, A. Kumar and R.T. Walker, *Tetrahedron Letts.*, 1988, **29**, 835.

93. T. Takeda, S. Naito, K. Ando and T. Fujiwara, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 967.

94. S. Strecker, *Liebigs Ann. Chem.*, 1870, **155**, 177.

95. J.T. Edward and C. Jitrangsri, *Can. J. Chem.*, 1975, **53**, 3339.

96. J.C. Menéndez, G.G. Trigo and M.M. Söllhuber, *Tetrahedron Lett.*, 1986, **27**, 3285.

97. T. Hanafusa, J. Ichihara and T. Ashida, *Chem. Letts.*, 1987, 687.

98. M.P. Georgiadis and S.A. Haroutounian, *Synthesis*, 1989, 616.

99. S. Harusawa, Y. Hamada and T. Shioiri, *Tetraheron Lett.*, 1979, 4663.

100. K. Curry, M.J. Peet, D.S.K. Magnuson and H. McLennan, *J. Med. Chem.*, 1988, **31**, 864.

101. S.G. Davies and O. Ichihara, *Tetrahedron Asymm.*, 1991, **2**, 183.

102. S. Ram and L. Spicer, *Tetrahedron Lett.*, 1987, **28**, 515.

103. A.M. Felix, E.P. Heimer, T.J. Lambros, C. Tzougraki and J. Meienhofer, *J. Org. Chem.*, 1978, **43**, 4194.

104. B.M. Adger, C. O'Farrell, N.J. Lewis and M.B. Mitchell, *Synthesis*, 1987, 53.

105. J. Yoshimura, M. Yamamura, T. Suzuki and H. Hashimoto, *Chem. Lett.*, 983, 1001.

106. M. Yamamura, T. Suzuki, H. Hashimoto, J. Yoshimura, T. Okamoto and C.-G. Shin, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1413.

107. M.P. du Plessis, T.A. Modro and L.R. Nassimbeni, *J. Org. Chem.*, 1982, **47**, 2213.

108. H.O. House and L.F. Lee, *J. Org. Chem.*, 1976, **41**, 863.

109. K.B. Becker, M.K. Hohermuth and G. Rihs, *Helv. Chim. Acta*, 1982, **65**, 235.

110. P. Martin, H. Greuter, G. Rihs, T. Winkler and D. Bellus, *Helv. Chim. Acta*, 1981, **64**, 2571.

111. L.E. Overman, M.E. Okazaki and E. Jon Jacobsen, *J. Org. Chem.*, 1985, **50**, 2403.

112. S.G. Levine, *J. Am. Chem. Soc.*, 1958, **80**, 6150.

113. G. Wittig, W. Böll and K.-H. Krück, *Chem. Ber.*, 1962, **95**, 2514.

114. E.J. Corey and J.I. Shulman, *J. Org. Chem.*, 1970, **35**, 777.

115. C. Earnshaw, C.J. Wallis and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3099.

116. P. Magnuson and G. Roy, *J. Chem. Soc., Chem. Commun.*, 1979, 822.

117. A.S. Kende and T.J. Blacklock, *Tetrahedron Lett.*, 1980, **21**, 3119.

118. J. Moskal and A.M. van Leusen, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 137.

119. D. Rossi, A. Romeo and G. Lucente, *J. Org. Chem.*, 1978, **43**, 2576.

120. V.A. Solodenko, T.N. Kasheva, V.P. Kukhar, E.V. Kozlova, D.A. Mironenko and V.K. Svedas, *Tetrahedron*, 1991, **47**, 3989.

121. J.A. Dale, D.L. Dull and H.S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.

122. W.K. Joklik, *Herpesviruses*, Prentice Hall, Connecticut, 1985,

123. R.A. Smith, R.W. Sidwell and R.K. Robins, *Ann. Rev. Pharmacol. Toxicol.*, 1980, **20**, 259.

124. R.T. Walker and M.J. Gait, *Biosynthesis of nucleotides*, IRL Press at Oxford University Press, New York, 1990, 155.

125. J.S. Oxford and A. Galbraith, *Pharmacol. Ther.*, 1980, **11**, 181.

126. D.M. Zlyndikov, O.I. Kubar, T.P. Kovaleva and L.E. Kamforin, *Rev. Infect. Dis.*, 1981, **3**, 408.

127. A.J. Hay, A.J. Wolstenholme, J.J. Skehel and M.H. Smith, *EMBO Journal*, 1985, **4**, 3021.

128. J.L. Schulman, *Proc. Soc. Exp. Biol. Med.*, 1968, **128**, 1173.

129. J.S. Oxford, Plenum Press, 1984,

130. L.B. Allen, K.H. Boswell, A. Khwaga, R.B.J. Meyer, R.W. Sidewell, J.T. Witowski, L.F. Christensen and R.K. Robbins, *J. Med. Chem.*, 1978, **21**, 742.

131. M.J. Browne, *Antimicrob. Agents Chemother.*, 1979, **15**, 747.

132. B. Eriksson, E. Heglstrand, N.G. Johnsson, A. Larsson, A. Misiorny, J.O. Noren, L. Philipson, K. Stenberg, G. Stening, S. Stridh and B. Öberg, *Antimicrob. Agents Chemother.*, 1977, **11**, 946.

133. P.A. Furman, M.H. St Clair and T. Spector, *J. Biol. Chem.*, 1984, **259**, 9575.

134. J.C. Drach, *Purine nucleoside analogs as antiviral agents.*, Plenum, New York, 1984, 231.

135. J.C. Martin, C.A. Dvorak, D.F. Smee, T.R. Matthews and J.P. Verheyden, *J. Med. Chem.*, 1983, **26**, 759.

136. H. Nakashima, T. Matsui, S. Haradia, N. Kobayashi, A. Matsuda, T. Ueda and N. Yamamota, *Antimicrob. Agents Chemother.*, 1986, **90**, 933.

137. H. Mitsuya and S. Broder, *Proc. Natl Acad. Sci.*, 1986, **83**, 1911.

138. R. Yarchoan, H. Mitsuya, R.V. Thomas, J.M. Pluda, N.R. Hartman, C.-F. Perno, K.S. Marczyk, J.-P. Allain, D.G. Jones and S. Broder, *Science*, 1989, 412.

139. D.L. Taylor, L.E. Fellows, G.H. Farrar, R.J. Nash, D. Taylor-Robinson, M.A. Mobberly, T.A. Ryder, D.J. Jeffries and A.S. Tyms, *Antiviral Res.*, 1988, **10**, 11.

140. I.M. Jones and G.S. Jacob, *Nature*, 1991, **352**, 198.

141. G.W.J. Fleet, A. Karpas, R.A. Dwek, L.E. Fellows, A.S. Tyms, S. Petursson, S.K. Namgoong, N.G. Ramsden, P.W. Smith, J.C. Son, F. Wilson, D.R. Witty, G.S. Jacob and T.W. Rademacher, *FEBS Lett.*, 1988, **237**, 128.

142. H. Shimizu, H. Tsuchie, K. Yoshida, s. Morikawa, T. Tsuroka, H. Yamomoto, H. Ushijima and T. Kitamura, *AIDS*, 1990, **4**, 975.

143. A.S. Mildvan and L.A. Loeb, *C. R. C. Rev. Biochem.*, 1979, 219.

144. J.E. Coleman, *The role of Zn(II) in RNA and DNA polymerases.*, John Wiley & Sons, 1984,

145. C.F. Springgate, A.S. Mildvan, R. Abramson, J.L. Engle and L.A. Loeb, *J. Biol. Chem.*, 1973, **249**, 5987.

146. J.E. Coleman, *Biochem. Biophys. Res. Commun.*, 1974, **60**, 641.

147. J.S. Oxford and D.D. Perrin, *Ann. N. Y. Acad. Sci.*, 1977, **284**, 613.

148. P.A. Cload and D.W. Hutchinson, *Nucleic Acid Res.*, 1983, **11**, 5621.

149. D. Hamre, J. Bernstein and R. Donovick, *Proc. Soc. Exp. Biol. Med.*, 1950, **73**, 275.

150. D.J. Bauer, L. St. Vincent, L.H. Kempe and A.M. Downie, *Lancet*, 1963, **2**, 494.

151. J.S. Oxford and D.D. Perrin, *J. Gen. Virol.*, 1974, **23**, 59.

152. W. Brockman, R.W. Sidwell, G. Arnett and S. Shaddix, *Proc. Exp. Biol. Med.*, 1970, **133**, 609.

153. N.L. Shipkowitz, R.R. Bower, R.N. Appell, C.W. Nordeen, L.R. Overby, W.R. Roderick, J.B. Schleicher and A.M. Von Esch, *Appl. Microbiol.*, 1973, **26**, 264.

154. D.W. Hutchinson, *Antiviral Res.*, 1985, **5**, 193.

155. S. Stridh and R. Datema, *Virology*, 1984, **135**, 293.

156. H. Fleisch, *Drugs*, 1991, **42**, 919.

157. R.P. Spencer and F. Hosain, *Bone Pharmaceuticals*, CRC Press, Florida, 1986, **II**, 127.

158. G.L. Plosker and K.L. Goa, *Drugs*, 1994, **47**, 945.

159. A.A. Licata, *Cleveland Clin. J. Med.*, 1993, **60**, 284.

160. T.S.T. Wang, R.A. Fawaz, L.J. Johnson, G.E. Mojdehi and P.M. Johnson, *J. Nucl. Med.*, 1980, **21**, 767.

161. J.C.-H. Mao, E.R. Otis, A.M. von Esch, T.R. Herrin, J.S. Fairgrieve, N.L. Shipkowitz and R.G. Duff, *Antimicrob. Agents Chemother.*, 1985, **27**, 197.

162. D.W. Hutchinson, M. Naylor and G. Semple, *Chem. Scipta*, 1986, **26**,

163. D.W. Hutchinson and M. Naylor, *Nucleic Acids Res.*, 1985, **13**, 8514.

164. F.A. Cotton and A. Wilkinson, *Inorganic Chemistry*, Wiley, New York, 1980, 73.

165. G.M. Blackburn, *Chem. Ind. (London)*, 1981, 134.

166. D.W. Hutchinson, M. Naylor and P.M. Cullis, *Antiviral Res.*, 1985, **5**, 67.

167. R.G. Pearson, *Science*, 1966, **151**, 172.

168. D. Thornton, PhD Thesis, University of Warwick, 1989.

169. G.M. Kosolapoff, *J. Am. Chem. Soc.*, 1953, **75**, 1500.

170. F.A. Cotton and R.A. Schun, *J. Am. Chem. Soc.*, 1963, **85**, 2394.

171. O.T. Quimby, J.D. Curry, D.A. Nicholson, J.B. Prentice and C.H. Roy, *J. Organomet. Chem.*, 1968, **13**, 199.

172. D.W. Hutchinson and G. Semple, *J. Organomet. Chem.*, 1985, **291**, 145.

173. D.W. Hutchinson and D.M. Thorton, *Synthesis*, 1990, 135.

174. R.K. Singh and S. Danishefsky, *J. Org. Chem.*, 1975, **40**, 2969.

175. E.V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 170.

176. J. Dockx, *Synthesis*, 1973, 441.

177. A. Brändström and U. Junggren, *Acta Chem. Scand.*, 1969, **23**, 2204.

178. M. Makosza and E. Bialecka, *Tetrahedron Lett.*, 1971, **12**, 4517.

179. I. Tabushi, Y. Aoyama and N. Takahashi, *Tetraheron Lett.*, 1973, 107.

180. R. Neidlein and T. Eichinger, *Monat. Chem.*, 1992, **123**, 1037.

181. J.R. Hanrahan and D.W. Hutchinson, *Tetrahedron Lett.*, 1993, **34**, 3767.

183. P. Gmeiner, P.L. Feldman, M.Y. Chu-Moyer and H. Rapport, *J. Org. Chem.*, 1990, **3068**,

184. D.A. Evans and A.E. Weber, *J. Am. Chem. Soc.*, 1986, **106**, 6757.

185. R. Noyori and M. Kitamura, *Angew. Chem. Int. Ed. Engl*, 1991, **30**, 49.

186. K. Soai and S. Niwa, *Chem. Rev.*, 1992, **92**, 833.

187. T. Sato, K. Soai and T. Mukaiyama, *Chem. Lett.*, 1978, 601.

188. N. Oguni and T. Omi, *Tetrahedron Lett.*, 1984, **25**, 2823.

189. R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, N. Oguni, M. Hayashi, T. Kaneko and Y. Matasuda, *J. Organomet. Chem.*, 1990, **382**, 19.

190. C. Bolm, J. Müller, G. Schlingloff, M. Zehnder and M. Neuburger, *J. Chem. Soc., Chem. Commun.*, 1993, 182.

191. K. Soai, Y. Hirose and Y. Ohno, *Tetrahedron Asymm.*, 1993, **4**, 1473.

192. S.G. Pyne, P. Bloem, S.L. Chapman, D.E. Dixon and R. Griffith, *J. Org. Chem.*, 1989, **55**, 1086.

193. F. Rebiere, O. Samuel, L. Ricard and H.B. Kagan, *J. Org. Chem.*, 1991, **56**, 5991.

194. R. Devant, U. Mahler and M. Braun, *Chem. Ber.*, 1987, **121**, 397.

195. M. Mikolajczyk, W. Midura, A. Miller and M. Wieczorek, *Tetrahedron*, 1987, **43**, 2967.

196. M.R. Barbachyn and C.R. Johnson, *Optical Activation and Utilization of compounds Containing Chiral Sulfur Centres.*, Academic Press, Orlando, 1984, **4**, 227.

197. P. Pitchen, E. Duñach, M.N. Deshmukh and H.B. Kagan, *J. Am. Chem. Soc.*, 1984, **106**, 8188.

198. D.C. Bradley, R.C. Mehrota and D.P. Gaur, *Metal Alkoxides*, Academic Press, London, 1978.

199. J. Kopf, W.P. Lorenzen and E. Weiss, *Chem. Ber.*, 1988, **121**, 1201.

200. D.D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chenicals*, Pergamon Press, Oxford.

Appendix 1

Table 1. Crystal Data and Structure Refinement for *Z*-Diethyl 3-(Phenylacetoxy)-3-cyanocyclobutanephosphonate

Empirical formula	$C_{17}H_{22}NO_5P$
Formula weight	351.33
Temperature	220(2) K
Wavelength	0.71073Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 9.991(5)Å alpha = 90 deg. b = 12.885(8)Å beta = 90 deg. c = 28.39(2)Å gamma = 90 deg.
Volume	3655(4)Å^3
Z	8
Density (calculated)	1.277 Mg/m^3
Absorption coefficient	0.175 mm^{-1}
F(000)	1488
Crystal size	0.49 x 0.34 x 0.29 mm
Theta range for data collection	2.49 to 22.54 deg.
Index ranges	0<=h<=10, 0<=k<=13, -1<=l<=30
Reflections collected	3798
Independent reflections	2405 [R(int) = 0.0366]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2400/8/217
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1=0.0854, wR2=0.2242
R indices (all data)	R1=0.1471, wR2=0.2954
Largest diff. peak and hole	0.481 and -0.750 e.Å^{-3}

Table 2. **Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.**

	x	y	z	U(eq)
P(1)	1665(2)	2763(1)	3655(1)	47(1)
O(1)	1073(5)	2402(4)	5609(2)	58(1)
O(2)	-309(4)	1795(3)	5050(2)	46(1)
O(3)	3017(5)	3201(4)	3638(2)	63(2)
O(4)	1599(5)	1556(3)	3740(2)	51(1)
O(5)	914(5)	2974(4)	3181(2)	61(2)
N(1)	-1420(7)	4258(5)	5230(3)	74(2)
C(1)	671(6)	3243(5)	4124(2)	43(2)
C(2)	1249(6)	3056(6)	4625(2)	48(2)
C(3)	-163(7)	2775(5)	4799(3)	49(2)
C(4)	-630(6)	2666(5)	4284(2)	41(2)
C(5)	2343(8)	-252(5)	5946(3)	58(2)
C(6)	3226(8)	-512(6)	6302(4)	73(3)
C(7)	3010(8)	-174(7)	6754(3)	77(3)
C(8)	1932(8)	457(7)	6849(3)	78(3)
C(9)	1052(7)	734(6)	6497(3)	62(2)
C(10)	1243(7)	375(5)	6040(2)	48(2)
C(11)	242(8)	648(5)	5666(3)	55(2)
C(12)	413(7)	1725(6)	5456(3)	45(2)
C(13)	-850(7)	3604(6)	5051(3)	50(2)
C(14)	2669(10)	861(7)	3593(3)	72(2)
C(15)	2457(13)	515(7)	3112(3)	100(4)
C(16)	-404(8)	2559(7)	3073(3)	73(3)
C(17)	-675(12)	2742(9)	2562(3)	111(4)

Table 3. Bond lengths [Å] and angles [deg] for Diethyl 3-(*O*-Phenylacetoxy)-3-cyanocyclobutanephosphonate

P(1)-O(3)	1.464(5)
P(1)-O(5)	1.566(5)
P(1)-O(4)	1.575(5)
P(1)-C(1)	1.772(7)
O(1)-C(12)	1.178(8)
O(2)-C(12)	1.363(8)
O(2)-C(3)	1.458(8)
O(4)-C(14)	1.455(9)
O(5)-C(16)	1.454(9)
N(1)-C(13)	1.137(8)
C(10)-C(5)	1.390(8)
C(10)-C(9)	1.391(8)
C(10)-C(11)	1.500(10)
C(5)-C(6)	1.382(9)
C(6)-C(7)	1.372(8)
C(7)-C(8)	1.375(8)
C(8)-C(9)	1.377(9)
C(11)-C(12)	1.519(9)
C(3)-C(13)	1.457(10)
C(3)-C(2)	1.537(9)
C(3)-C(4)	1.541(10)
C(4)-C(1)	1.566(9)
C(1)-C(2)	1.555(9)
C(14)-C(15)	1.450(11)
C(16)-C(17)	1.494(11)
O(3)-P(1)-O(5)	110.3(3)
O(3)-P(1)-O(4)	115.1(3)
O(5)-P(1)-O(4)	106.5(3)
O(3)-P(1)-C(1)	114.0(3)
O(5)-P(1)-C(1)	108.4(3)
O(4)-P(1)-C(1)	101.9(3)
C(12)-O(2)-C(3)	114.7(5)
C(14)-O(4)-P(1)	122.2(5)
C(16)-O(5)-P(1)	123.5(5)
C(5)-C(10)-C(9)	118.7(7)
C(5)-C(10)-C(11)	121.9(6)
C(9)-C(10)-C(11)	119.5(6)
C(6)-C(5)-C(10)	120.4(6)
C(7)-C(6)-C(5)	120.4(7)
C(6)-C(7)-C(8)	119.6(8)
C(7)-C(8)-C(9)	120.7(7)
C(8)-C(9)-C(10)	120.2(6)
C(10)-C(11)-C(12)	114.6(6)
O(1)-C(12)-O(2)	124.0(7)
O(1)-C(12)-C(11)	126.5(7)

O(2)-C(12)-C(11)	109.5(6)
C(13)-C(3)-O(2)	110.3(6)
C(13)-C(3)-C(2)	114.6(6)
O(2)-C(3)-C(2)	116.8(5)
C(13)-C(3)-C(4)	113.0(6)
O(2)-C(3)-C(4)	110.8(5)
C(2)-C(3)-C(4)	89.8(5)
N(1)-C(13)-C(3)	176.9(9)
C(3)-C(4)-C(1)	88.9(5)
C(2)-C(1)-C(4)	88.2(5)
C(2)-C(1)-P(1)	115.2(5)
C(4)-C(1)-P(1)	121.2(5)
C(3)-C(2)-C(1)	89.4(5)
C(15)-C(14)-O(4)	110.6(8)
O(5)-C(16)-C(17)	108.1(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. **Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$**

	U11	U22	U33	U23	U13	U12
P(1)	36(1)	43(1)	63(1)	0(1)	6(1)	-4(1)
O(1)	49(3)	51(3)	73(3)	0(3)	-17(3)	-14(3)
O(2)	31(3)	37(3)	70(3)	5(2)	-3(3)	-3(2)
O(3)	44(3)	68(3)	77(4)	-4(3)	13(3)	-32(3)
O(4)	46(3)	36(3)	73(3)	-8(2)	10(3)	6(2)
O(5)	59(3)	57(3)	69(3)	0(3)	-3(3)	-9(3)
N(1)	66(5)	51(4)	106(6)	-8(4)	33(5)	14(4)
C(1)	31(4)	32(3)	65(5)	10(3)	0(4)	-1(3)
C(2)	27(4)	48(4)	68(5)	-2(4)	10(4)	2(3)
C(3)	30(4)	34(4)	84(6)	3(4)	10(4)	-3(3)
C(4)	25(4)	41(4)	57(4)	-5(3)	-5(3)	0(3)
C(5)	55(5)	47(4)	72(5)	-16(4)	15(5)	-12(4)
C(6)	45(5)	55(5)	119(8)	-3(5)	-12(6)	9(4)
C(7)	59(6)	82(7)	90(7)	13(6)	-32(6)	5(5)
C(8)	65(6)	103(8)	65(6)	0(5)	-2(5)	17(6)
C(9)	44(5)	74(5)	68(5)	1(4)	2(5)	11(4)
C(10)	41(4)	45(4)	57(5)	-2(4)	-2(4)	-8(4)
C(11)	52(5)	53(5)	60(5)	-3(4)	-10(4)	-20(4)
C(12)	25(4)	45(4)	63(5)	-14(4)	4(4)	1(4)
C(13)	30(4)	45(4)	76(5)	8(4)	9(4)	-5(4)
C(14)	79(6)	69(5)	68(6)	-2(5)	8(5)	21(5)
C(15)	147(10)	75(7)	77(6)	14(5)	31(7)	2(7)
C(16)	56(5)	81(6)	82(6)	7(5)	-20(5)	-12(5)
C(17)	110(9)	136(10)	86(7)	-6(7)	-37(7)	-11(8)

Table 5. **Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for 1.**

	x	y	z	U(eq)
H(1)	485(6)	3991(5)	4077(2)	51
H(2A)	1882(6)	2476(6)	4641(2)	57
H(2B)	1625(6)	3679(6)	4773(2)	57
H(4A)	-1459(6)	3042(5)	4214(2)	49
H(4B)	-685(6)	1945(5)	4176(2)	49
H(5)	2489(8)	-500(5)	5639(3)	70
H(6)	3976(8)	-927(6)	6236(4)	88
H(7)	3595(8)	-369(7)	6998(3)	93
H(8)	1796(8)	700(7)	7157(3)	93
H(9)	318(7)	1161(6)	6569(3)	74
H(11A)	-655(8)	598(5)	5804(3)	66
H(11B)	301(8)	131(5)	5414(3)	66
H(14A)	3527(10)	1226(7)	3615(3)	87
H(14B)	2700(10)	258(7)	3803(3)	87
H(15A)	3173(13)	50(7)	3019(3)	149
H(15B)	2445(13)	1112(7)	2905(3)	149
H(15C)	1607(13)	154(7)	3092(3)	149
H(16A)	-1086(8)	2906(7)	3265(3)	87
H(16B)	-433(8)	1814(7)	3142(3)	87
H(17A)	-1579(12)	2521(9)	2489(3)	166
H(17B)	-44(12)	2348(9)	2374(3)	166
H(17C)	-580(12)	3475(9)	2492(3)	166

Appendix 2

Table 1. Crystal Data and Structure Refinement for *E*-Diethyl 3-(*N*-*p*-Methoxybenzylamino)-3-cyanocyclobutanephosphonate

Empirical formula	$C_{17}H_{25}N_2O_4P$
Formula weight	352.36
Temperature	220(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a=7.630(3) Å α =94.09(4) deg. b=9.882(5) Å β=104.07(3) deg. c=13.604(6) Å γ=99.27(4) deg.
Volume	975.4(8) $Å^3$
Z	2
Density (calculated)	1.200 Mg/m^3
Absorption coefficient	0.162 mm^{-1}
F(000)	376
Crystal size	0.78 x 0.22 x 0.12 mm
Theta range for data collection	1.55 to 25.05 °
Index ranges	0<=h<=9, -11<=k<=11, -16<=l<=15
Reflections collected	3728
Independent reflections	443[R(int)=0.0548]
Absorption correction	Analytical
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3441/8/225
Goodness-of-fit on F^2	1.045
Final R indices [I>2σ(I)]	R1=0.0538, wR2=0.1554
R indices (all data)	R1=0.0675, wR2=0.1728
Extinction coefficient	0.033(6)
Largest diff. peak and hole	0.523 and -0.312 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
P(1)	4010(1)	3127(1)	6540(1)	47(1)
O(1)	2466(3)	2949(2)	7008(2)	67(1)
O(2)	4663(3)	4664(2)	6360(2)	61(1)
O(3)	3673(3)	2299(2)	5460(2)	65(1)
O(4)	15423(2)	114(2)	11735(1)	54(1)
N(1)	10145(3)	2902(2)	8481(2)	40(1)
N(2)	10238(4)	6251(3)	7861(2)	71(1)
C(1)	6014(3)	2586(3)	7234(2)	43(1)
C(2)	7778(3)	2907(3)	6856(2)	47(1)
C(3)	8837(3)	3664(2)	7922(2)	39(1)
C(4)	7014(3)	3482(3)	8262(2)	46(1)
C(5)	9628(3)	5128(3)	7887(2)	48(1)
C(6)	4270(6)	5882(4)	6887(3)	82(1)
C(7)	3151(7)	6600(5)	6163(3)	106(2)
C(8)	2170(6)	2434(6)	4627(3)	111(2)
C(9)	1827(10)	1205(8)	3883(5)	189(3)
C(10)	11100(3)	3576(3)	9512(2)	46(1)
C(11)	12281(3)	2679(2)	10100(2)	40(1)
C(12)	11539(3)	1627(3)	10581(2)	47(1)
C(13)	12597(3)	783(3)	11109(2)	48(1)
C(14)	14477(3)	984(2)	11179(2)	41(1)
C(15)	15254(3)	2023(2)	10705(2)	43(1)
C(16)	14154(3)	2865(2)	10173(2)	43(1)
C(17)	17319(4)	199(3)	11751(2)	54(1)

Table3. Bond lengths [Å] and angles [deg] for Diethyl 3-(*N*-*p*-Methoxybenzylamino)-3-cyanocyclobutanephosphonate

P(1)-O(1)	1.462(2)
P(1)-O(3)	1.571(2)
P(1)-O(2)	1.575(2)
P(1)-C(1)	1.775(3)
O(2)-C(6)	1.466(4)
O(3)-C(8)	1.434(4)
O(4)-C(14)	1.363(3)
O(4)-C(17)	1.430(3)
N(1)-C(3)	1.448(3)
N(1)-C(10)	1.469(3)
N(2)-C(5)	1.138(4)
C(1)-C(2)	1.549(3)
C(1)-C(4)	1.551(4)
C(2)-C(3)	1.548(3)
C(3)-C(5)	1.484(4)
C(3)-C(4)	1.557(3)
C(6)-C(7)	1.446(5)
C(8)-C(9)	1.471(7)
C(10)-C(11)	1.499(3)
C(11)-C(12)	1.384(4)
C(11)-C(16)	1.389(3)
C(12)-C(13)	1.372(4)
C(13)-C(14)	1.395(3)
C(14)-C(15)	1.380(3)
C(15)-C(16)	1.391(3)
O(1)-P(1)-O(3)	116.15(13)
O(1)-P(1)-O(2)	113.69(13)
O(3)-P(1)-O(2)	103.45(12)
O(1)-P(1)-C(1)	114.95(12)
O(3)-P(1)-C(1)	101.59(12)
O(2)-P(1)-C(1)	105.50(12)
C(6)-O(2)-P(1)	124.8(2)
C(8)-O(3)-P(1)	121.3(2)
C(14)-O(4)-C(17)	117.7(2)
C(3)-N(1)-C(10)	113.2(2)
C(2)-C(1)-C(4)	90.1(2)
C(2)-C(1)-P(1)	117.8(2)
C(4)-C(1)-P(1)	114.9(2)
C(3)-C(2)-C(1)	89.9(2)
N(1)-C(3)-C(5)	113.7(2)
N(1)-C(3)-C(2)	112.5(2)
C(5)-C(3)-C(2)	112.8(2)
N(1)-C(3)-C(4)	112.5(2)
C(5)-C(3)-C(4)	113.3(2)
C(2)-C(3)-C(4)	89.9(2)

C(1)-C(4)-C(3)	89.5(2)
N(2)-C(5)-C(3)	179.8(2)
C(7)-C(6)-O(2)	110.2(3)
O(3)-C(8)-C(9)	107.2(4)
N(1)-C(10)-C(11)	111.2(2)
C(12)-C(11)-C(16)	117.7(2)
C(12)-C(11)-C(10)	121.1(2)
C(16)-C(11)-C(10)	121.2(2)
C(13)-C(12)-C(11)	121.8(2)
C(12)-C(13)-C(14)	119.9(2)
O(4)-C(14)-C(15)	124.6(2)
O(4)-C(14)-C(13)	115.8(2)
C(15)-C(14)-C(13)	119.6(2)
C(14)-C(15)-C(16)	119.5(2)
C(11)-C(16)-C(15)	121.5(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$

	U11	U22	U33	U23	U13	U12
P(1)	36(1)	65(1)	42(1)	11(1)	10(1)	10(1)
O(1)	42(1)	102(2)	66(1)	23(1)	23(1)	16(1)
O(2)	71(1)	63(1)	62(1)	19(1)	31(1)	24(1)
O(3)	52(1)	88(2)	46(1)	-6(1)	-1(1)	15(1)
O(4)	48(1)	55(1)	61(1)	25(1)	13(1)	13(1)
N(1)	38(1)	44(1)	40(1)	2(1)	12(1)	12(1)
N(2)	71(2)	52(2)	91(2)	15(1)	23(2)	12(1)
C(1)	38(1)	51(1)	39(1)	9(1)	10(1)	6(1)
C(2)	39(1)	64(2)	38(1)	1(1)	11(1)	9(1)
C(3)	33(1)	49(1)	36(1)	6(1)	11(1)	9(1)
C(4)	36(1)	68(2)	36(1)	7(1)	12(1)	11(1)
C(5)	42(1)	56(2)	50(1)	9(1)	14(1)	14(1)
C(6)	107(3)	76(2)	74(2)	12(2)	33(2)	34(2)
C(7)	147(4)	112(3)	88(3)	37(2)	46(3)	73(3)
C(8)	85(3)	158(4)	71(2)	-11(3)	-18(2)	38(3)
C(9)	179(6)	184(6)	129(5)	-72(4)	-79(4)	40(5)
C(10)	45(1)	46(1)	42(1)	-2(1)	4(1)	13(1)
C(11)	37(1)	44(1)	38(1)	-2(1)	7(1)	8(1)
C(12)	33(1)	53(2)	54(2)	3(1)	14(1)	4(1)
C(13)	43(1)	49(1)	52(1)	12(1)	16(1)	1(1)
C(14)	40(1)	41(1)	40(1)	6(1)	8(1)	6(1)
C(15)	31(1)	47(1)	51(1)	9(1)	11(1)	4(1)
C(16)	40(1)	40(1)	49(1)	11(1)	13(1)	5(1)
C(17)	44(1)	49(2)	64(2)	10(1)	3(1)	14(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for Diethyl 3-(*O*-Phenylacetoxy)-3-cyanocylobutanephosphonate

	x	y	z	U(eq)
H(1)	10881(37)	2741(26)	8160(20)	41(7)
H(1A)	5744(3)	1599(3)	7335(2)	51
H(2A)	8239(3)	2082(3)	6668(2)	56
H(2B)	7674(3)	3511(3)	6312(2)	56
H(4A)	7050(3)	2978(3)	8859(2)	55
H(4B)	6566(3)	4346(3)	8353(2)	55
H(6A)	3623(6)	5597(4)	7400(3)	98
H(6B)	5426(6)	6501(4)	7238(3)	98
H(7A)	2785(43)	7342(24)	6526(4)	159
H(7B)	2064(25)	5961(10)	5769(19)	159
H(7C)	3853(18)	6981(32	5708(18)	159
H(8A)	2482(6)	3272(6)	4314(3)	133
H(8B)	1072(6)	2493(6)	4869(3)	133
H(9A)	944(79)	1325(33)	3264(22)	283
H(9B)	1341(93)	399(14)	4167(23)	283
H(9C)	2969(23)	1081(43)	3726(42)	283
H(10A)	10192(3)	3778(3)	9876(2)	55
H(10B)	11867(3)	4453(3)	9466(2)	55
H(12)	10276(3)	1488(3)	10544(2)	56
H(13)	12054(3)	71(3)	11422(2)	57
H(15)	16517(3)	2160(2)	10742(2)	52
H(16)	14691(3)	3575(2)	9856(2)	51
H(17A)	17824(8)	-475(14)	12167(13)	81
H(17B)	17989(6)	1118(7)	12037(14)	81
H(17C)	17429(4)	10(20)	11062(3)	81